

**CENTRE FOR RESEARCH COLLECTIONS
EDINBURGH UNIVERSITY LIBRARY
GEORGE SQUARE
EDINBURGH
EH8 9LJ
TEL: +44 (0)131 650 8379
FAX: +44 (0)131 650 2922**

BOOK-SCANNED 2014

**AUTHOR: Howard, James Keir
TITLE: Paraquat – in use and misuse
SHELF MARK: M.D. 1982**

N.B.

Scanned as single pages.

Blank pages have been omitted.

Orientation of copy as it appears in the original.

THIS IS THE BEST COPY AVAILABLE

© Edinburgh University Library

This PDF is supplied for the purpose of research and private study.
No reproductions or further copies may be made without prior permission from
Edinburgh University Library.

Please address all enquiries to Centre for Research Collections.

The Library wishes to be informed of work based on this Pdf copy, and would
welcome a copy of any publication that makes use of it.

The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336

PARAQUAT - IN USE AND MISUSE

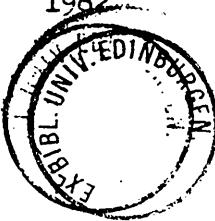
by

JAMES KEIR HOWARD

M.D. THESIS

UNIVERSITY OF EDINBURGH

1982



CONTENTS

	Page
ACKNOWLEDGEMENTS 	iv
ABSTRACT 	v
1 GENERAL INTRODUCTION 	1
1.1 THE SCOPE OF THE THESIS 	2
1.2 THE PROPERTIES AND MODE OF ACTION OF PARAQUAT	6
1.2.1 GENERAL PROPERTIES 	6
1.2.2 ASPECTS OF PARAQUAT PHARMACOKINETICS	12
1.2.3 THE MODE OF ACTION OF PARAQUAT ...	19
1.2.4 THE PATHOGENESIS OF PARAQUAT LUNG INJURY AND OTHER EFFECTS 	28
1.3 REFERENCES 	32
APPENDIX 1.1: PRODUCTS CONTAINING PARAQUAT ...	41
2 THE OCCUPATIONAL USE OF PARAQUAT AND ASSOCIATED RISKS	42
2.1 PATTERNS OF USE AND EXPOSURE 	43
2.2 LOCAL TOXIC EFFECTS 	50
2.2.1 CUTANEOUS EFFECTS 	50
2.2.2 EPISTAXIS 	53
2.2.3 NAIL DAMAGE 	54
2.2.4 EYE INJURY 	56
2.3 SYSTEMIC TOXICITY FROM USE 	58
2.3.1 GENERAL OBSERVATIONS 	58
2.3.2 ORAL INGESTION 	61
2.3.3 DERMAL ABSORPTION 	63
2.3.4 INHALATION 	71

CONTENTS (Continued)

		Page
2.4	INVESTIGATIONS OF OCCUPATIONAL EXPOSURE ...	79
2.4.1	FORMULATION WORKERS	79
2.4.2	LONG TERM PARAQUAT SPRAYING ...	89
2.4.3	COMPARATIVE RISKS FROM HIGH AND LOW VOLUME SPRAYING TECHNIQUES	116
2.5	CONCLUSIONS	128
2.6	REFERENCES	131
APPENDIX 2.1:	REGRESSION EQUATIONS FOR CLINICAL MEASUREMENTS	137
APPENDIX 2.2:	MALAYSIAN SPRAY WORKER STUDY - INDEPENDENT VARIABLES	138
APPENDIX 2.3:	MALAYSIAN SPRAY WORKER STUDY - RESPIRATORY FUNCTION VALUES ...	139
APPENDIX 2.4:	MALAYSIAN SPRAY WORKER STUDY - HAEMATOLOGY VALUES	140
APPENDIX 2.5:	MALAYSIAN SPRAY WORKER STUDY - LIVER FUNCTION VALUES	141
3	THE MISUSE OF PARAQUAT: THE PROBLEM OF ACCIDENTAL AND INTENTIONAL POISONING	142
3.1	THE EXTENT OF THE PROBLEM	143
3.1.1	ACCIDENTAL POISONING	145
3.1.2	DELIBERATE SELF POISONING ...	149
3.2	APPROACHES TO THERAPY	157
3.2.1	INDICATIONS FOR ACTIVE TREATMENT ...	159
3.2.2	TREATMENT METHODS	161
	THE PREVENTION OF ABSORPTION ...	161
	THE REMOVAL OF PARAQUAT FROM THE CIRCULATION	166
	THE USE OF 'ANTI-PARAQUAT' THERAPY	169

CONTENTS (Continued)

		Page
3.3	THE EFFECTIVENESS OF THERAPY	173
3.3.1	LENGTH OF SURVIVAL IN FATAL POISONING.	173
3.3.2	RECOVERY RELATED TO THE TIME TREATMENT WAS INSTITUTED, TREATMENT METHOD AND INGESTED DOSE	176
3.4	REFERENCES	198
4	CONCLUDING OBSERVATIONS	207
4.1	PARAQUAT IN USE	209
4.2	PARAQUAT IN MISUSE	211
4.3	REFERENCES	214
5	SELECT BIBLIOGRAPHY	215

ACKNOWLEDGEMENTS

A large number of people have been involved in the studies reported in this thesis and there is a sense in which it is invidious to single out individuals. Particularly grateful thanks and appreciation, however, are due to the following:

Dr S Prasan, Pattaya, South Thailand; Dr N N Sabapathy, Chief Medical Officer, Dunlop Estates Sdn Bhd, Melaka, Malaysia; Mrs P A Whitehead, Statistician, ICI Ltd, Plant Protection Division, Bracknell, UK and Mr G Chesters, Environmental Toxicologist, ICI Ltd, Central Toxicology Laboratory, Alderley Park, UK for their invaluable help in the execution of the clinical studies.

Appreciative thanks are also due to: Dr Roy Goulding, lately Director, National Poisons Information Service and the Poisons Unit, Guys Hospital, London; Dr L L Smith, Senior Toxicologist, ICI Ltd, Central Toxicology Laboratory, Alderley Park, UK; Dr K S Williamson, Director of Medical Services, ICI Ltd, Wilmslow, UK; and Dr A T Proudfoot, Director, Poisons Unit, Royal Infirmary, Edinburgh who was also appointed the author's advisor by the University, who all made helpful comments and criticisms during the preparation of this thesis.

ABSTRACT

This thesis sets out to examine the problems that have been associated with paraquat, both in relation to its occupational use as a herbicide and its misuse in cases of accidental or deliberate human poisoning. In order to provide a frame of reference for the later discussion, the general properties of paraquat are reviewed, together with its general toxic effects and possible mode of action in mammalian systems.

The degree of risk associated with paraquat use in normal agricultural practice is examined. The available published literature is reviewed and the results of studies on both formulation workers and spraymen are discussed. It is concluded that the use of paraquat does not constitute a significant risk to health when sprayed at concentrations of up to 0.5% paraquat ion. Studies of situations in which low volume/high concentration application methods have been used would indicate that they are likely to produce an unacceptable level of risk and constitute dangerous agricultural practice.

The problem of paraquat misuse is examined, both in regard to its extent and the effectiveness of treatment in cases of human poisoning. Treatment measures currently advocated are reviewed and their effectiveness discussed in relation to the series of 108 poisoning cases which is presented. On the basis of the data set out it is concluded that the treatment of paraquat poisoning is only likely to be

ABSTRACT (Continued)

effective in those cases who have,

- (a) ingested less than 5g of paraquat ion,
- (b) had treatment instituted within 2 hours of ingestion, and
- (c) show plasma paraquat levels in the order of 1-2mg/litre 2-4 hours after ingestion.

It is also concluded that the only effective form of treatment is the vigorous and rapid removal of paraquat from the gut using Fuller's Earth and purgation or gut lavage. There is little clinical evidence to suggest that measures designed to remove paraquat from the circulation after absorption or block its action in the body have any effect on the clinical course of poisoning.

Some general conclusions are drawn and a select bibliography is appended.

SECTION I

GENERAL INTRODUCTION

1. GENERAL INTRODUCTION

1.1. THE SCOPE OF THE THESIS

The herbicide paraquat is a member of a group of compounds known as quaternary bipyridyls. It was first synthesised in the nineteenth century¹ and has been known to chemists and biochemists for many years on account of its properties as a redox indicator dye, used in the determination of the redox potentials of biological electron carriers²⁻⁵. In its partially reduced form as a free radical, paraquat possesses a deep blue colour which gives the compound its usefulness in such determinations (hence also the alternative name for paraquat of methyl viologen). It was not, however, until 1959 that its herbicidal properties became apparent which led to its commercial introduction as a weedkiller in the early 1960s⁶.

The wide spectrum of herbicidal activity, coupled with a remarkable lack of residual effect as a result of the compound's rapid inactivation on contact with the soil, led to the very wide application of paraquat throughout the world. The output of commercial formulations has been in millions of litres and in some parts of the world it has been responsible for the creation of a situation close to an agricultural revolution.

When paraquat was first marketed, the manufacturers did not apparently anticipate any particular problems with its use, although its general level of toxicity was greater than that of

most herbicides being applied in agriculture (table 1.1. provides a comparison of acute oral and dermal LD₅₀'s for a number of standard herbicides). It soon became apparent, however, that the compound could be subject to serious misuse by accidental or deliberate ingestion which was seen to be associated with particularly unpleasant consequences. These were highlighted by the first reported cases of human poisoning⁷. It is not surprising, therefore, that considerable disquiet has been expressed about this compound, particularly in view of the high mortality which has followed ingestion of the commercial formulations, the distressing form of death following both accidental and deliberate poisoning, together with the fact that children have at times been the tragic victims of accidental poisoning incidents. Indeed, it was the early accidental deaths, occurring soon after the commercial introduction of paraquat, that occasioned the greatest reaction, especially in the press. The introduction in the United Kingdom of governmental regulation of the sale and purchase of the agricultural concentrates on the one hand, together with an educational programme for the public (more especially farmers and horticulturists) on the other, led to a shift in the nature of the problem. Accidental cases became fewer, as will be discussed later, but (possibly as a result of the widespread publicity) intentional poisonings increased in number.

This thesis is an attempt to set the problems associated with paraquat into a realistic context. Two areas of concern will be reviewed, the occupational use of the compound as a herbicide

TABLE 1.1 COMPARATIVE TABLE OF ACUTE ORAL AND DERMAL LD₅₀
VALUES FOR A NUMBER OF STANDARD HERBICIDES

Herbicide	LD ₅₀ values (mg/kg)	
	Oral	Dermal
Aminotriazole	1100	10 000
Atrazine	1850	7 500
2,4-D	375	-
Dalapon	7570	-
Paraquat	160	236

Oral values are for rat; dermal values for rabbit

Source: WORTHING C R, (Ed), The Pesticide Manual,

Croydon, British Crop Protection Council, 1979

and the accidental or deliberate misuse of the compound in cases of human poisoning. The approach will be as follows:

1. The question of whether paraquat poses a significant risk to spray operators in normal agricultural practice will be examined first. The available literature will be reviewed and the results of the author's studies on formulation workers and on spray workers using both standard and low-volume application methods will be discussed.
2. Secondly, there will be an attempt to examine the extent of the problem of accidental and deliberate human poisoning with paraquat. The various approaches to treatment will be examined and an attempt made to assess the effectiveness of those treatment measures currently advocated, based largely on the author's studies of 108 cases of human poisoning.

1.2. THE PROPERTIES AND MODE OF ACTION OF PARQUAT

In order to provide a framework for the later consideration of those problems associated with both the normal occupational use of paraquat in agriculture and the misuse of the compound in cases of human poisoning, it is necessary to provide an outline of the main properties of this material. This section will thus set out to describe briefly the physico-chemical properties of paraquat and then go on to describe those aspects of the pharmacokinetics which are relevant to human poisoning, together with a short account of the biochemical mechanism of action and resultant pathological changes in order to relate the toxicity of paraquat to current modes of treatment of poisoning.

1.2.1 GENERAL PROPERTIES

The physico-chemical properties of paraquat are set out in table 1.2. There are several routes of synthesis of the compound (summarised by Haley⁸), of which the most usual for commercial preparations leads to the production of the dichloride salt and is in two stages. The first involves the coupling of two molecules of pyridine to produce 4,4'-bipyridyl in the presence of sodium in anhydrous ammonia. This is then quaternized with methyl chloride to produce the dichloride salt of paraquat⁹. These reactions are shown graphically in fig 1.1.

The relative insolubility of paraquat in hydrocarbon and other

TABLE 1.2: PHYSICO-CHEMICAL PROPERTIES OF PARAQUAT

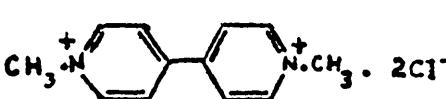
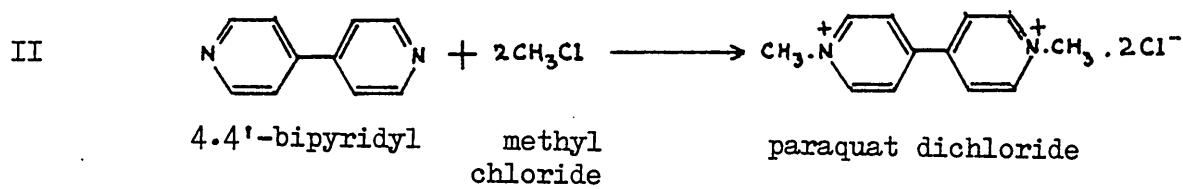
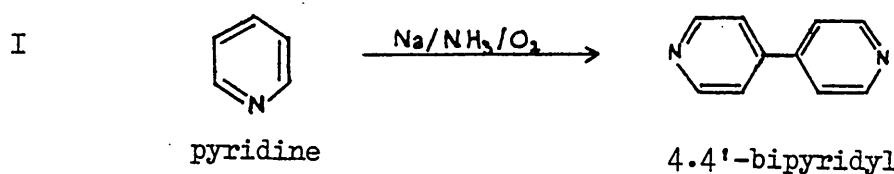
Common name:	Paraquat (dichloride)
Chemical name:	1,1'-dimethyl-4,4'-bipyridinium dichloride
Structural formula:	
Molecular formula:	C ₁₂ H ₁₄ N ₂ Cl ₂
Molecular weight:	257 (as dichloride) 186 (as cation)
Specific gravity:	1.24-1.26 (20/20)
Melting point:	175-180°C
Decomposition point:	Approximately 300°C
Appearance:	Colourless to yellowish crystalline needles
Solubility:	Highly soluble in water with complete dissociation into paraquat cations and chloride anions. Low solubility in alcohol and insoluble in hydrocarbon-based organic solvents.
Stability:	Stable in acid and neutral aqueous solution. Gradually hydrolyzes in alkaline solution.
Vapour pressure:	Below limit of measurement: nonvolatile solid.
Other properties:	Highly corrosive to metals. Non-explosive. Non-flammable.

FIG 1.1: STEPS IN THE SYNTHESIS OF PARAQUAT DICHLORIDE

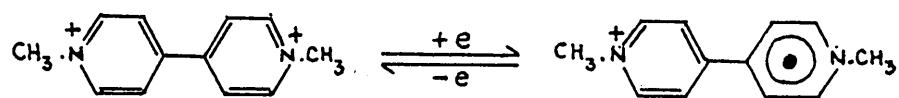


commonly used organic solvents has led to its being marketed as water based formulations, usually with either 10 or 20 percent (w/v) of paraquat ion as the active ingredient. Appendix 1.1 lists the currently available commercial formulations of paraquat marketed by ICI Ltd. In addition to those produced by ICI Ltd there are a large number of other formulations produced principally in Taiwan, some of which are based on the dichloride salt and others on the methyl sulphate. Such commercial preparations are usually maintained at pH 7.0 (± 0.5) to ensure the stability of the product, although this is not true of all non-ICI formulations.

In solution, paraquat cation may be readily reduced by the addition of one electron to form a relatively stable, water soluble free radical which is blue/purple in colour. This free radical has a maximum absorption at 396 nm and this fact forms the basis of the spectrophotometric methods of analysis¹⁰. The reduction step to the free radical is pH independent and consists in the addition of a single electron to the bivalent paraquat ion to produce a partially reduced monovalent cation. The formation of the free radical may be achieved electrochemically, by chemical reducing agents (including biochemical redox systems) and also by a photolytic process in the presence of primary or secondary alcohols. The reaction is readily reversible and is represented in fig 1.2.

A feature of this and similar reactions of the class of radicals

FIG 1.2: REDUCTION OF PARAQUAT TO THE FREE RADICAL



known as 'violenes' is the distribution of an odd number of electrons (in this case one) on an even number of atoms and is known as resonance delocalisation. It is believed to be responsible for the relative stability of the paraquat free radical ^{11, 12}. The relative ease of free radical formation by single electron reduction is a property of the redox potential of the molecule (in the case of paraquat $E_{\circ} = 446$ mV) and this also is an important determining factor for the phytotoxic properties of the bipyridyl series, especially in regard to the light dependent reduction reactions. Ledwith has recently reviewed these reduction reactions of paraquat ¹³. Of particular importance toxicologically are the rapid reactions of the paraquat free radical with molecular oxygen to reform the cation which will be discussed later (see 1.2.2).

Paraquat also undergoes a virtually irreversible base exchange with the cations of the various components of soil, especially the clay constituents. It also undergoes similar reactions with a variety of ion-exchange resins. Such reactions explain the rapid inactivation of paraquat in soil, as a result of its combining with clay particles and as will be discussed later, also point to the usefulness of clay suspensions in the treatment of paraquat poisoning ^{11, 14, 15}. Paraquat is also decomposed by direct sunlight and this photochemical degradation plays an important part in the fate of the herbicide in the environment⁹.

1.2.2. ASPECTS OF PARAQUAT PHARMACOKINETICS

There are three aspects of the general pharmacokinetics of paraquat that are of particular relevance to the problem of human poisoning and its treatment. These are: the rate of absorption from the gut after ingestion, the selective uptake of paraquat by the lung and the renal clearance of the compound.

(a) Absorption of paraquat from the gut

It has been generally accepted that paraquat is poorly absorbed from the mammalian gut, over 80 percent being egested in the faeces and only 4 to 11 percent being excreted by the kidneys over the first four days after ingestion^{16,17}. Peak concentrations are usually reached in the plasma within six hours of ingestion, depending on the animal species used, and usually the amount of circulating paraquat is at or below the limit of detection by 24 to 48 hours¹⁸. Although there is little information with regard to the absorption of paraquat by humans, it has been generally assumed that only about 5 percent of the ingested dose is absorbed¹⁸.

It is clear, however, that not all animal work can be directly extrapolated to man. This applies particularly to results from rats and other rodents, although it is on these species that most of the experimental work has been performed. Smith and his co-workers¹⁵ showed an almost linear relationship

between gut content of paraquat and plasma levels, with the plasma concentrations remaining remarkably constant for up to 30 hours. In contrast, the plasma levels in dogs¹⁹ (also L.L. Smith 1980, personal communication) and monkeys (L.L. Smith 1980, personal communication) show a rapid and very marked rise after oral dosing, peaking at about 2 to 3 hours after ingestion and falling rapidly thereafter (fig 1.3). Potentially lethal amounts of paraquat thus enter the circulation more rapidly than in the rat and the pattern of human poisoning in those cases in which serial measurements of plasma paraquat have been made²⁰ suggests that the dog and monkey are better models of events for the human situation than the rat. Fig 1.4 shows serial plasma levels in four recent, and hitherto unpublished, cases of human poisoning. In each case plasma levels were beginning to fall by the time the first blood samples were taken, indicating a peak plasma level within two hours of ingestion and the bulk of absorption taking place within four hours. Proudfoot and his collaborators have shown similar findings in their series²⁰. Such a time scale, with most absorption taking place within four hours of ingestion, will clearly have an important bearing on the efficacy of any measures taken to reduce the amount of absorption from the gut in cases of poisoning.

(b) Concentration of paraquat in the lung

It is generally agreed that paraquat is not significantly metabolised in the mammal¹⁶. The tissue distribution after absorption has been studied by a number of workers and it has

FIG 1.3: COMPARATIVE PARAQUAT PLASMA CONCENTRATIONS
IN THREE ANIMAL SPECIES AFTER ORAL DOSING

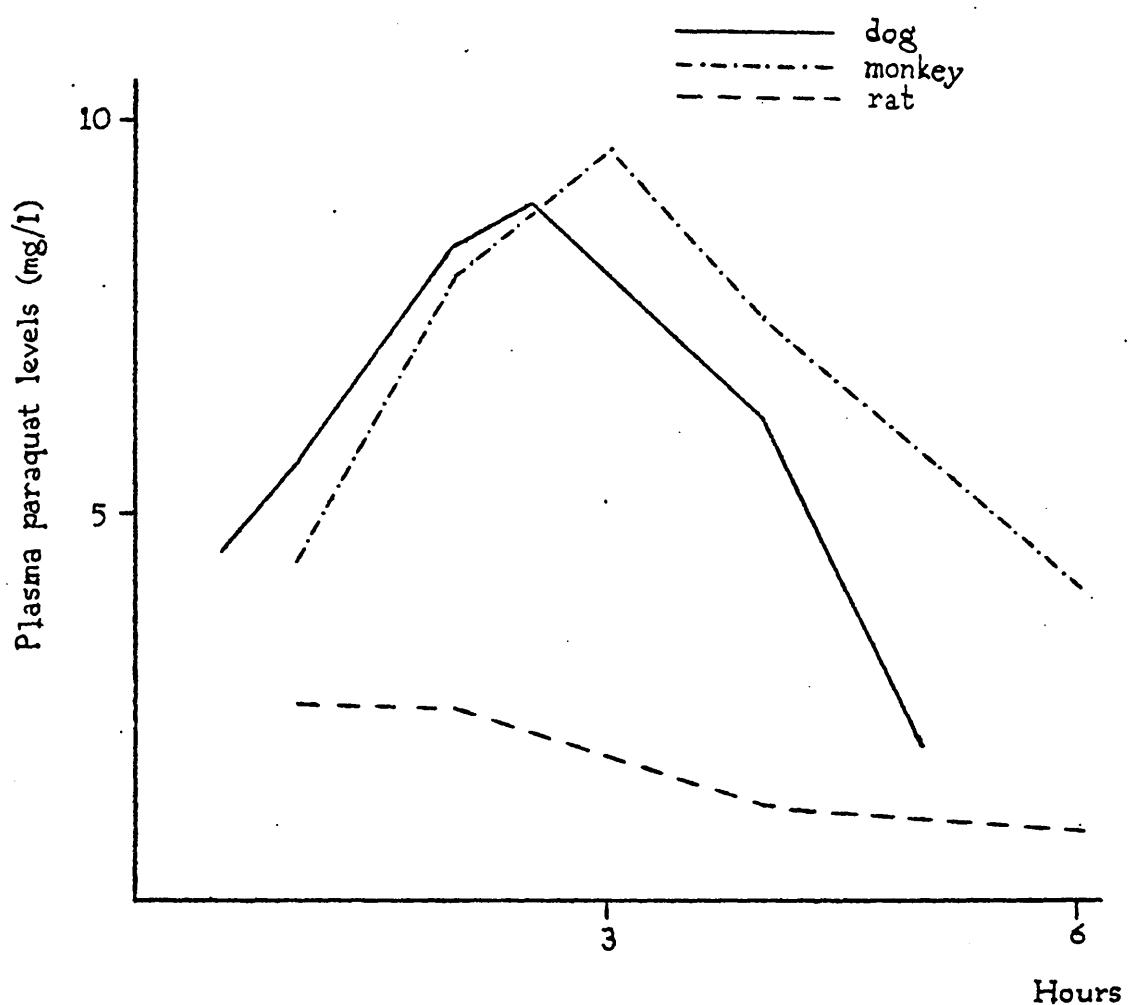
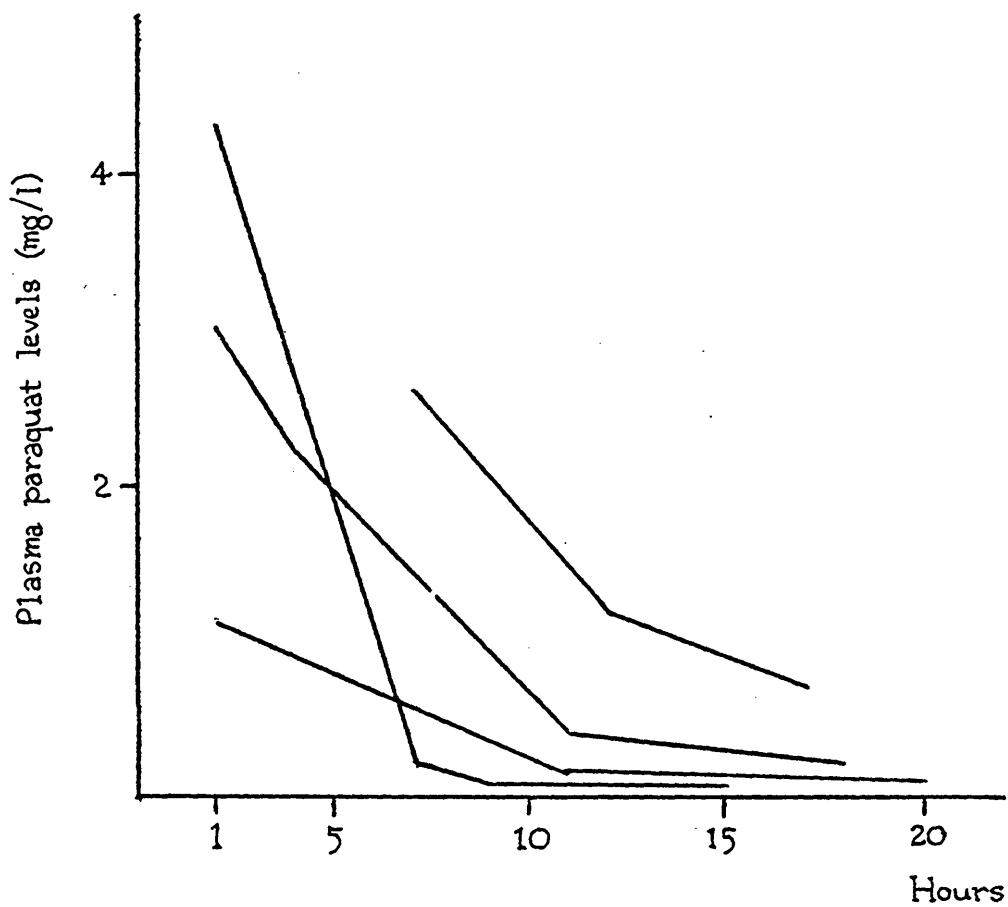


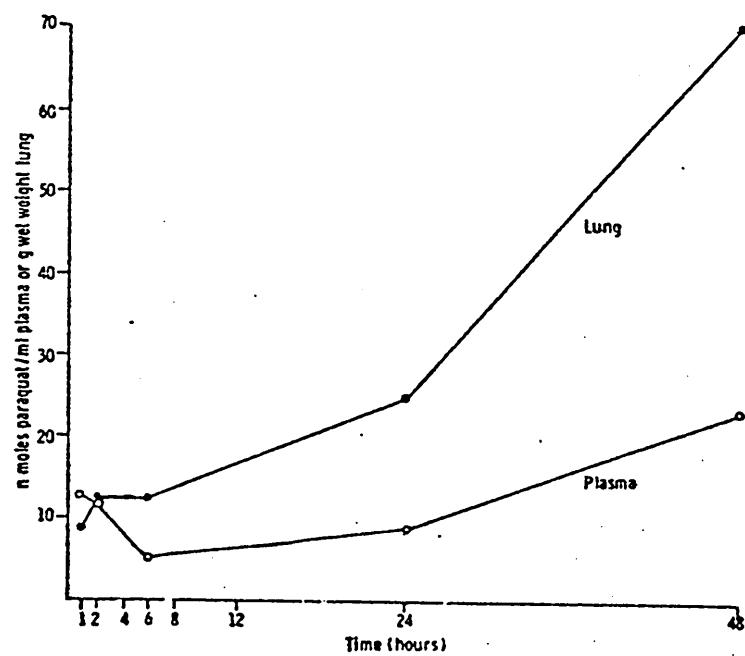
FIG 1.4 SERIAL PLASMA PARAQUAT CONCENTRATIONS
IN FOUR PATIENTS FOLLOWING DELIBERATE
INGESTION



been effectively demonstrated that paraquat, unlike other members of the bipyridyl family, such as diquat and morfamquat, is selectively concentrated in the lungs of all species, compared with other tissues²¹⁻²³. Rose and his colleagues²⁴ were able to show that both the plasma and renal levels of paraquat following an initial rise remained very constant after oral dosing in the rat, but that the concentrations in the lung increased with time throughout the duration of the study. By 30 hours after dosing the lung concentrations had reached levels that were some six or seven times higher than those of other tissues (fig 1.5).

The mechanism responsible for this accumulation has not so far been identified, but it has been shown to be energy dependent²⁵ and unrelated to any binding phenomena^{23, 26}. A variety of endogenous amines and amino acids are able to inhibit paraquat accumulation in vitro as are also a number of exogenous compounds including d-propranolol^{25, 26}. The sites of accumulation appear to be predominantly the type I and type II alveolar cells. Sykes and his co-workers²⁷ showed that within 4 hours from intravenous dosing there was evidence of ultra-structural change in these cells which was progressive so that by 16 hours damage was significant. Similar accumulation has been shown to occur in human lungs in vitro¹⁵ and the kinetics of uptake seem to be very similar to those found in the rat. This peculiarity of the lung would explain its ability to take up paraquat over a long period of time from very low plasma concentrations and it would also account for the prominence of lung injury in poisoning cases.

FIG. 1.5. PARAQUAT CONCENTRATIONS IN PLASMA AND LUNG
OF RATS AFTER DOSING WITH 680 $\mu\text{mol}/\text{kg}$.



(Data provided by L.L. Smith)

(c) Renal excretion of paraquat

A number of clearance studies have been undertaken with paraquat in dogs 19, 28, 29, 30, showing that paraquat clearance was normally in excess of creatinine clearance and that it appeared to be independent of the plasma concentration over a wide range. It seems possible that some passive re-absorption takes place in the proximal half of the nephron, together with active secretion. The latter is indicated by the rapid excretion of low doses at clearance rates above the glomerular filtration rate³⁰. It is unlikely, however, that the re-absorption is particularly effective¹⁹ and consequently there is little evidence that forced diuresis would be an effective means of removing paraquat from the circulation.

The effect of paraquat on the kidney appears to be limited to the proximal tubules. Functional damage follows evidence of tubular cell necrosis with induction of both smooth endoplasmic reticulum (SER) and lipidic cytosomes as early changes^{31,32}. A similar induction of SER has been noted following administration of cephaloridine, a pyridine containing antibiotic. It is possible that the renal toxicity of paraquat is related to its pyridine-based structure.

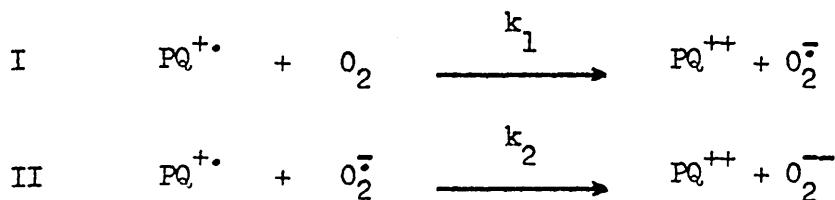
In the dog it has been shown that the plasma and renal concentrations closely parallel one another, with the peak being reached at about 90 minutes after ingestion, thus demonstrating an effective quantitative renal clearance provided that no renal

damage has occurred^{19, 30}. Where such damage has taken place, however, the decline in concentrations in plasma and urine do not run in parallel once the peak has been passed. The plasma concentration lags behind at a higher level, thus allowing the lung to accumulate the material selectively over a long period. The degree of renal damage appears to be dose-related and it has been suggested that early renal failure would increase the uptake in the lung by a factor of five³⁰. The evidence suggests that this situation closely parallels that occurring in human poisoning³³. It has been shown in man that the relationship between paraquat and creatinine clearance remains constant where the kidney is not damaged³⁴, but that the clearance of paraquat falls rapidly once tubular damage has been induced¹⁹. Thus the time of onset and the degree of renal damage in such cases must be viewed as an important determinant of the ultimate lung concentrations and subsequent outcome of poisoning.

1.2.3. THE MODE OF ACTION OF PARAQUAT

The phytotoxic actions of paraquat, together with its mammalian toxicity, are to a very large extent functions of the ability of the free radical to react readily with molecular oxygen. In the green plant paraquat appears to function as a catalytic co-factor in the overall photoreduction of molecular oxygen to peroxidic species. The available evidence suggests that it is the superoxide (O_2^-) and peroxide(O_2^-) radicals that are responsible for the phytotoxicity of the bipyridyl herbicides³⁵. The essentials of the reactions in which the free radical ($PQ^{+•}$)

is oxidised back to the bivalent paraquat cation (PQ^{++}) are as follows³⁶:



The energy necessary for this process to proceed in plants is derived from photosynthesis, a series of reactions that generates a flow of electrons which are, in turn, transported by a variety of physiological carriers. The end result of the process is the formation of a series of energy-rich compounds such as ATP and reduced NADP^+ . Because of its redox potential paraquat is able to compete with the natural electron acceptors in the cell and it is probably reduced by the same mechanisms which reduce NADP^+ during photosynthesis, such as ferredoxin.

The free radicals thus formed are very rapidly re-oxidised by molecular oxygen back to the parent cation which is thus available for further reduction. This catalytic type reaction shunts the electron flow of photosynthesis or mitochondrial respiration into its own redox cycle, thus depleting cellular energy reserves. At the same time, however, it is also generating a constant flow of superoxide and peroxide radicals which themselves have an immediate toxic action on the plant tissues. These processes have been discussed in detail by Calderbank and Slade⁹, Calderbank¹¹ and Akhavein and Linscott¹².

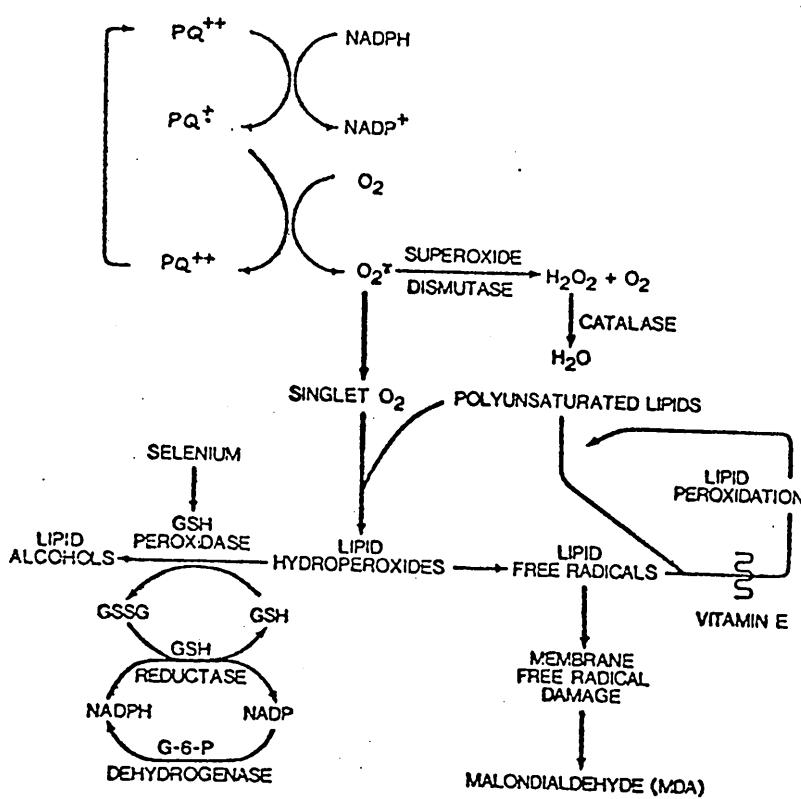
The biochemical mode of action of paraquat in mammals, including man, appears to be analogous to its mode of action in plants.

The detailed mechanisms that have been proposed have been reviewed in depth by Haley⁸, Pasi³⁷ and Smith et al²⁶.

It is thus only necessary for an outline to be provided here.

The initial biochemical event is the production of the paraquat free radical (PQ^+), a reaction requiring the presence of NADPH as an electron donor and which, in vitro at least, proceeds until equilibrium has been reached^{38, 39}. NADPH acts essentially as a co-factor in this series of reactions, passing its two electrons to FAD^+ , thus producing FADH . The latter is the prosthetic group of an enzyme from which paraquat in turn takes an electron to form the free radical³⁸. Under normal aerobic conditions this process is likely to involve a cyclic oxidation and reduction of the paraquat free radical, involving NADPH and the cytochrome system^{40, 41}. It is, however, the stage beyond the formation of the free radical about which there is continuing debate. There are two main hypotheses. One, advocated strongly by Bus and his colleagues⁴¹⁻⁴⁵, considers that the major toxic effects are the result of lipid peroxidation, that is, the oxidative deterioration of polyunsaturated lipids. It is postulated that, as cell membranes contain a high proportion of unsaturated lipids and are thus liable to peroxidative damage, the process of lipid peroxidation induces loss of membrane integrity and ultimately cell death. The mechanism that Bus and his co-workers have proposed is shown graphically in fig 1.6.

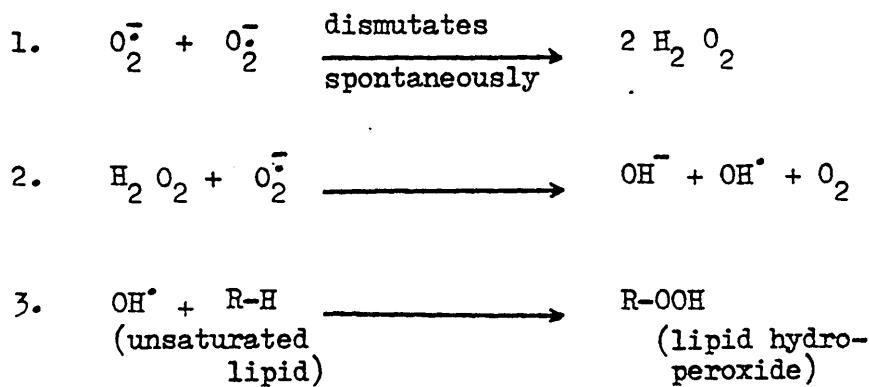
FIG 1.6: PROPOSED MECHANISM FOR PARAQUAT TOXICITY



(Derived from Bus, et al: ref 44).

The cyclic reduction and oxidation of paraquat, dependent on NADPH, produces the superoxide radical as noted earlier. This rapidly dismutates to singlet oxygen which being a highly reactive molecule attacks the unsaturated lipids of the cell membrane to produce lipid hydroperoxides⁴⁶. These decompose spontaneously in the presence of trace amounts of metal ions to initiate a chain reaction of lipid peroxidation and ultimately cell death, as set out in fig 1.6.

This view is not universally accepted, however. Smith and his co-workers (L.L. Smith 1981, personal communication) believe that a more likely mechanism for lipid peroxidation, if in fact it occurs at all, is as a consequence of hydroxyl (OH^{\bullet}) attack on unsaturated lipids (R-H), rather than as an effect of singlet oxygen. The sequence of reactions are taken from Haber-Weiss cycle and is referred to as Fenton toxicity:



The scheme proposed by Bus also suggests three possible intracellular defence mechanisms which in theory, might prevent the damaging effects of lipid peroxidation on the cell membrane. Firstly, it is postulated that there would be

a rapid conversion of superoxide radicals to molecular oxygen and hydrogen peroxide, a reaction catalysed by the enzyme superoxide dismutase⁴⁷. This enzyme is considered to be of cardinal importance as a defence mechanism against attack by superoxide radicals⁴⁸, effectively lowering the O_2^- concentration so that the reaction



cannot proceed. The hydrogen peroxide is detoxified by conversion to water by the action of glutathione peroxidase or catalase. The value of this mechanism in real terms is a moot point, however. It has been shown that rats acutely dosed with paraquat die more rapidly in high ambient concentrations of oxygen than they would in normal atmospheric concentrations⁴⁹. Lung microsomes exposed to paraquat show a marked stimulation of the formation of both superoxide radicals and hydrogen peroxide⁵⁰ and, although Crapo and Tierney⁵¹ observed an induction of superoxide dismutase in rat lungs after exposure to high oxygen concentrations, Montgomery has demonstrated a marked deficiency of the enzyme in lung microsomes after exposure to paraquat⁵². Such a deficiency might be an additional factor in the pulmonary specificity of paraquat toxicity.

Indeed, the picture that is emerging of paraquat poisoning is one that closely parallels the mechanism and effects of oxygen poisoning. The primary toxic event in this situation is thought to be the generation of O_2^- from the mitochondria.

As the concentration of oxygen increases so is the likelihood of O_2^- being produced. When paraquat and oxygen act together in high concentrations, as in the study of Fisher and his colleagues⁴⁹, then more O_2^- is produced, firstly by the $PQ^{++} \rightleftharpoons PQ^+$ cycling and secondly by mitochondrial generation.

In a very real sense paraquat poisoning may be considered as a chemically-induced form of oxygen toxicity.

Secondly, it has been proposed that the various endogenous antioxidants within the cell such as tocopherols (vitamin E) and ascorbic acid which terminate peroxidative chain reactions may well have an important role to play in breaking the cyclic formation of lipid hydroperoxides⁵³⁻⁵⁵. In addition, the enzyme glutathione peroxidase which reduces unstable lipid hydroperoxides to stable lipid alcohols would be able to break the cyclic production of more free radicals⁵⁶. Selenium has been shown to play a part in glutathione peroxidase activity⁵⁷ which may, in part at least, account for the antioxidant properties of this metal. It has been shown that selenium deficient rats are more susceptible to paraquat poisoning than normal animals⁵⁸ although the animals in this particular study died from liver lesions rather than from an effect on the lung. The reducing equivalents for the action of glutathione peroxidase in detoxifying the increased levels of tissue lipid hydroperoxides are derived from the cyclic reduction and oxidation of glutathione and NADPH, reactions mediated by the enzymes glutathione reductase and glucose 6-phosphate dehydrogenase⁵⁹. This mechanism probably has a wide role in detoxification mechanisms

as the author has demonstrated in respect of heavy metals⁶⁰ and recent observations suggest that reduced activity of this enzyme is associated with an increased sensitivity to paraquat toxicity^{60a}. These proposed defense mechanisms at the cellular level have led to attempts to improve the outcome in poisoning cases by a variety of innovations in therapy and management. They will be discussed in Section 3 in relation to the problem of human poisoning.

An alternative hypothesis to that of lipid peroxidation has been proposed by Smith, Rose and their co-workers and the main elements of their proposed scheme has been set out in an extended review of the subject²⁶. The essential feature of their view is that the basic toxic mechanism of paraquat is a depletion of cellular energy reserves as a result of the oxidation of NADPH⁶¹. The rate of oxidation is very fast, particularly in those cells in which paraquat is accumulated, as in the lung. If the rate of oxidation outstrips the rate of formation, then the concentration of NADPH will fall below that required to maintain vital processes, resulting in the death of the cell.

Some recent studies have provided confirmation of this hypothesis. The oxidation of NADPH is an early and prominent biochemical event in the lungs of rats after oral dosing with paraquat and the ratio of NADPH to NADP⁺ is markedly reduced within the cells^{62,63}. In mammalian cells the major biochemical process for the reduction of NADP⁺ to NADPH is considered to be the pentose phosphate pathway. The activity of this pathway has been shown to be markedly stimulated in lung slices incubated with paraquat in vitro and

in the lungs of paraquat poisoned rats^{61, 61a}. Further evidence for the 'NADPH-depletion' hypothesis is provided by the fact that fatty acid synthesis in the lung is inhibited by paraquat.

The synthesis of fatty acids is dependent on NADPH⁶⁴ and may well be of particular importance in the type II alveolar epithelial cells as they are involved in the synthesis of pulmonary surfactant⁶⁵. Incubation of lung slices with paraquat inhibited fatty acid synthesis, but this inhibition could be abolished by the addition of putrescine to the incubation medium, this compound being an effective blocker of paraquat accumulation into the lung^{61, 70}.

Such a mechanism would also enhance the toxicity of the superoxide radicals formed by the reduction/oxidation cycle of paraquat since it has been postulated that oxygen toxicity itself is mediated through the extreme oxidation of NADPH leading to the formation of lipid peroxides⁶⁶. In such a situation the cellular concentrations of NADPH would first be reduced by the formation of the paraquat free radical and then secondly, they would be further depleted by the defense mechanism against lipid hydroperoxides. The lipid peroxidation would thus be secondary to cellular depletion of NADPH rather than the primary toxic reaction as proposed by Bus and his colleagues. It seems reasonable to assume however, that both mechanisms may be involved in the overall toxic attack of paraquat on the cell.

It should also be noted that as the phosphate pentose cycle is stimulated to regenerate NADPH in response to the action of

paraquat⁶⁷⁻⁷⁰, this co-factor becomes available, not only for the conversion of oxidised glutathione to the reduced form, but also for the further production of paraquat free radicals. It is postulated that in these circumstances the attempts by the cell to replace NADPH in order to enhance the detoxification mechanisms serves only to contribute further to the toxic response. The cellular damage occurring as a result of such metabolic processes is a sufficient cause in itself for the fibroblastic response so prominent in the lung, which has been regarded as no more than the standardepithelial response to injury. Paraquat-induced lung injury thus has two distinct phases and the pathogenesis of the lung effects, together with the effects of paraquat on other organ systems will now be discussed briefly.

1.2.4 THE PATHOGENESIS OF PARAQUAT LUNG INJURY AND OTHER EFFECTS

(a) Lung Injury

The two phases of lung damage to which allusion has already been made, may be categorised as destructive and proliferative. A number of extensive animal studies have been performed, notably by Vijayaratnam and Corrin⁷¹. They were able to show that, with dose levels close to the LD₅₀, there was evidence of damage to the type I and type II alveolar epithelial cells within the first day after dosing. This process continued rapidly, so that by the end of four days after dosing there was complete destruction of areas of alveolar epithelium. At the same time there was extensive exudation into the alveolar air spaces with haemorrhage. Throughout this destructive phase there was marked infiltration by inflammatory cells into the alveolar inter-

stitial space, the air spaces and the perivascular areas. This inflammatory exudative response grossly reduces the alveolar gaseous exchange and the great majority of animals dying in the early phase as the result of an LD₅₀ did so from severe anoxia ⁷².

The second, proliferative phase, developed in the survivors of the initial destructive phase. This stage was characterised by an extensive fibroblastic proliferation with attempts to regenerate and restore the normal architecture of the alveolar epithelium ⁷¹. The greatest proliferation of fibroblasts, however, was in the interstitial spaces, which, together with residual oedema and alveolar collapse, resulted in severe anoxia and ultimately death.

Similar changes in the lung have been observed post mortem in cases of human paraquat poisoning ^{73, 74}. The primary phase has been described as an attack on alveolar capillaries leading to haemorrhage, oedema, the extrusion of pulmonary phagocytes and dilatation of respiratory bronchioles. Deposition of fibrin also occurs in the oedema fluid at this early stage. The phagocytes appear to undertake a scavenging role and there is some evidence that they may be responsible for the removal of surfactant ⁷⁴. It is unlikely that they are fibroblastic precursors as suggested by Smith and Heath ^{73, 75}, particularly in view of their abrupt disappearance with time. The proliferative changes of the second phase may occur as early as the eighth day after ingestion, but are more usually found later than 17 days ⁷⁶. These changes are a mixture of a diffuse interstitial fibrosis with resultant compression and obliteration of alveolar spaces, together with a

variable degree of intra-alveolar fibrosis derived from the reticulum deposition of the first phase.

The evidence from human poisoning cases supports the view outlined previously, that the lung fibrosis, which is such a prominent feature of late surviving cases of paraquat poisoning, is no more than an exaggerated reparative response. Furthermore, the post mortem appearances of the lung, coupled with the evidence for phagocytic scavenging of surfactant^{74, 77} is very much the picture found in hyperbaric oxygen poisoning, a condition that has been described as 'lung surfactant deficit syndrome'⁷⁸. This lends weight to the hypothesis, derived initially from a consideration of the biochemical mechanism of toxicity, that paraquat poisoning is to be viewed as essentially a form of chemically induced oxygen poisoning.

The biphasic lung response has implications for treatment which will be discussed in detail later in section 3.

(b) Other Effects

Immediately after the ingestion of the concentrated formulations of paraquat there may be ulceration of the mouth and oesophagus^{79, 80} as a result of the caustic/irritant properties of the material. Large doses may lead to proximal tubular renal necrosis⁸¹ and centrilobular hepatocellular necrosis^{82, 83}. Large doses may also be associated with adrenal corticonecrosis⁸⁴⁻⁸⁶ and, less commonly, with oedema and haemorrhage of the brain⁸⁷. Such cases have usually died in the early acute phase after massive doses, often

within 48 hours of poisoning, but the adreno-cortical effects have been observed with smaller doses and over a longer period⁸⁶. The implications of the wider organ involvement will be discussed later.

1.3 REFERENCES

- 1 WEIDEL H, RUSSO M, Studien über das pyridin. Monatsch Chim 1882; 3 : 850-855
- 2 MICHAELIS L, HILL E S, Potentiometric studies on semiquinones. J Amer Chem Soc 1933; 55 : 1481-1494
- 3 MICHAELIS L, HILL E S, The viologen indicators. J Gen Physiol 1933; 16 : 859-870
- 4 GEST H, PECK H D, Study of the hydrogenlyase reaction with systems derived from normal and anaerogenic coliaerogenes bacteria. J Bacteriol 1955; 70 : 326
- 5 WHITELEY H R, ORDAL E J, Reduction of methylene blue by hydrogenase. J Bacteriol 1955; 70 : 508
- 6 HOMER R F, MEES G C, TOMLINSON T E, Mode of action of dipyrindyl quaternary salts as herbicides. J Sci Food Agric 1960; 11 : 309-315
- 7 BULLIVANT C M, Accidental poisoning by paraquat: Report of two cases. Brit Med J 1966; 1 : 1272-1273
- 8 HALEY T J, Review of the toxicology of paraquat. Clin Toxicol 1979; 14 : 1-46
- 9 CALDERBANK A, SLADE P, Diquat and paraquat. In: Herbicides: Degradation and Mode of Action. Kearney P C, Kaufmann D D, (eds). New York, Dekker. 2nd Edition, 1976. 501-540.
- 10 YUEN S H, BAGNESS J E, MYLES D, Spectrophotometric determination of diquat and paraquat in aqueous herbicide formulations. Analyst 1967; 92 : 375
- 11 CALDERBANK A, The bipyridylum herbicides. Adv Rest Contr Res 1968 8 : 127-135

- 12 AKHAVEIN A A, LINSCOTT D I, The dipyridilium herbicides, diquat and paraquat. Residue Rev 1968; 23 : 97-145
- 13 LEDWITH A, Electron transfer reactions of paraquat. In: Biochemical Mechanisms of Paraquat Toxicity. Autor Anne P, (ed). New York, Academic Press, 1977. 21-38
- 14 KNIGHT B A G, TOMLINSON T E, The interaction of paraquat with mineral soils. J Soil Sci 1967; 18 : 233-243
- 15 SMITH L L, WRIGHT A, WYATT I, ROSE M S, Effective treatment for paraquat poisoning in rats and its relevance to the treatment of paraquat poisoning in man. Brit Med J 1974; 4 : 586-591
- 16 DANIEL J W, GAGE J C, Absorption and excretion of paraquat and diquat in rats. Brit J Indust Med 1966; 23 : 133-136
- 17 MURRAY R E, GIBSON J E, Paraquat disposition in rats, guinea pigs and monkeys. Toxicol Appl Pharmacol 1974; 27 : 283-291
- 18 CONNING D M, FLETCHER K, SWAN A A B, Paraquat and related bipyridyls. Brit Med Bull 1969; 25 : 245-249
- 19 DAVIES D S, HAWKSWORTH G M, BENNETT P N, Pharmacokinetic studies with paraquat. In: Clinical Aspects of Paraquat Poisoning. Fletcher K, (ed). London, ICI Ltd. 1975 81-84
- 20 PROUDFOOT A T, STEWART M S, LEVITT T, WIDDOP B, Paraquat poisoning : Significance of plasma-paraquat concentrations. Lancet 1979; i : 330-332
- 21 SHARP C W M, OTTOLENGHI A, POSNER H S, Correlation of paraquat toxicity with tissue concentration and weight loss of the rat. Toxicol Appl Pharmacol 1972; 22 : 241-251
- 22 LITCHFIELD M H, DANIEL J W, LONGSHAW S, The tissue distribution of the bipyridilium herbicides paraquat and diquat in rats and mice. Toxicology 1973; 1 : 155-163

- 23 ILETT K F, STRIPP B, MENARD R H, REID W D, GILLETTE J R,
Studies on the mechanism of the lung toxicity of paraquat:
Comparison of tissue distribution and some biochemical
parameters in rats and rabbits. Toxicol Appl Pharmacol
1974; 28 : 216-226
- 24 ROSE M S, LOCK E A, SMITH L L, WYATT I, Paraquat accumulation:
tissue and species specificity. Biochem Pharmacol 1976;
25 : 419-423
- 25 ROSE M S, SMITH L L, WYATT I, Evidence for the energy
dependent accumulation of paraquat in to rat lung. Nature
1974; 252 : 314-315
- 26 SMITH L L, ROSE M S, WYATT I, The pathology and biochemistry
of paraquat. In: Oxygen Free Radicals and Tissue Damage.
Ciba Foundation Series 65 (new series), Amsterdam, Excerpta
Medica, 1979. 321-341
- 27 SYKES B I, PURCHASE I F H, SMITH L L, Pulmonary ultra structure
after oral and intravenous dosage of paraquat to rats
J Pathol 1977; 121 : 233-241
- 28 FERGUSON D M, Renal handling of paraquat. Brit J Pharmacol
1971; 42 : 636P
- 29 FERGUSON D M, Factors influencing the renal excretion of
paraquat. Toxicol Appl Pharmacol 1973; 25 : 485
- 30 HAWKSWORTH G M, BENNETT P N, DAVIES D S, Kinetics of
paraquat elimination in the dog. Toxicol Appl Pharmacol
1981; 57 : 139-145
- 31 FOWLER B A, BROOKS R E, Effects of the herbicide paraquat
on the ultrastructure of the mouse kidney. Amer J Path
1971; 63 : 505-520

- 32 ECKER J L, HOOK J B, GIBSON J E, Nephrotoxicity of paraquat in mice. Toxicol Appl Pharmacol 1975; 34 : 178
- 33 WIDDOP B, MEDD R K, BRAITHWAITE R A, Charcoal haemoperfusion in the treatment of paraquat poisoning. Proc Europ Soc Toxicol 1977; 18 : 156-159
- 34 FISHER H K, HUMPHRIES M, BAILS R, Paraquat poisoning: Recovery from renal and pulmonary damage. Ann Int Med 1971; 75 : 731-736
- 35 DODGE A D, The mode of action of the bipyridylum herbicides, paraquat and diquat. Endeavour 1971; 30 : 130-135
- 36 FARRINGTON J A, EBERT M, LAND E J, FLETCHER K, Bipyridilium quaternary salts and related compounds. V. Pulse radiolysis studies on the reaction of paraquat radical with oxygen; Implications for the mode of action of bipyridilium herbicides. Biochem Biophys Acta 1973; 314 : 372-381
- 37 PASI A, The Toxicology of Parquat, Diquat and Morfamquat. Bern, Hans Huber, 1978
- 38 GAGE J C, The action of paraquat and diquat on the respiration of liver cell fractions. Biochem J 1968; 109 : 757-761
- 39 BALDWIN R C, PASI A, MCGREGOR J T, HINE C H, The rates of radical formation from the dipyridilium herbicides paraquat, diquat and morfamquat in homogenates of rat lung, kidney and liver: An inhibitory effect of carbon monoxide. Toxicol Appl Pharmacol 1975; 32 : 298-304
- 40 KREIGER R I, LEE P W, BLACK A, FUKUTO R T, Inhibition of microsomal aldrin epoxidation by diquat and several related bipyridilium compounds. Bull Environ Contam Toxicol 1973; 9 : 1-3

- 41 BUS J S, AUST S D, GIBSON J E, Superoxide and singlet oxygen catalysed lipid peroxidation as a possible mechanism for paraquat toxicity. Biochem Biophys Res Commun 1974; 58 : 749-755
- 42 BUS J S, AUST S D, GIBSON J E, Lipid peroxidation: A possible mechanism for paraquat toxicity. Res Commun Chem Path Pharmacol 1975; 11 : 31-38
- 43 BUS J S, GIBSON J E, Postnatal toxicity of chronically administered paraquat in mice and interaction with oxygen and bromobenzene. Toxicol Appl Pharmacol 1975; 33 : 461-470
- 44 BUS J S, CAGEN S Z, OLGAARD M, GIBSON J E, A mechanism of paraquat toxicity in mice and rats. Toxicol Appl Pharmacol 1976; 35 : 501-513
- 45 BUS J S, AUST S D, GIBSON J E, Lipid peroxidation as a proposed mechanism for paraquat toxicity. In: Biochemical Mechanisms of Paraquat Toxicity Autor Ann P, (ed). New York, Academic Press. 1976 157-174
- 46 PEDERSON T C, AUST S D, The role of superoxide and singlet oxygen in lipid peroxidation promoted by xanthine oxidase. Biochem Biophys Res Commun 1973; 52 : 1071-1078
- 47 McCORD J M, FRIDOVICH I, Superoxide dismutase: An enzymic function for erythrocuprein. J Biol Chem 1969; 244 : 6049-6055
- 48 FRIDOVICH I, Superoxide dismutases. Ann Rev Biochem 1975; 44 : 147-159
- 49 FISHER H K, CLEMENTS J A, WRIGHT R R, Enhancement of oxygen toxicity by the herbicide paraquat. Amer Rev Resp Dis 1973; 107 : 246-252

- 50 MONTGOMERY M R, Interaction of paraquat with the pulmonary microsomal fatty acid desaturase system. Toxicol Appl Pharmacol 1976; 36 : 543-554
- 51 CRAPO J D, TIERNEY D F, Superoxide dismutase and pulmonary oxygen toxicity. Amer J Physiol 1974; 226 : 1401-1407
- 52 MONTGOMERY M R, Paraquat toxicity and pulmonary superoxide dismutase: An enzymic deficiency of lung microsomes. Res Commun Chem Path Pharmacol 1977; 16 : 155-158
- 53 TAPPEL A L, Vitamin E and free radical peroxidation of lipids. Ann N Y Acad Sci 1972; 203 : 12
- 53a BLOCK E R, Potentiation of acute paraquat toxicity by Vitamin E deficiency. Lung 1979; 156 : 195-203
- 54 PIRIE A, REES J R, HOLMBERG N J, Diquat cataract: Formation of the free radical and its reaction with constituents of the eye. Exper Eye Res 1970; 9 : 204-218
- 55 LLOYD E L, Ascorbic acid and paraquat toxicity. Lancet 1976; ii : 1255
- 56 CHRISTOPHERSON B O, Reduction of linoleic acid hydroperoxide by a glutathione peroxidase. Biochem Biophys Acta 1969; 176 : 463-475
- 57 ROTRUCK J T, POPE A L, GANTHER H E, SWANSON A B, HAFEMAN D G, HOEKSTRA D G, Selenium: Biochemical role as a component of glutathione peroxidase. Science 1973; 179 : 588-595
- 58 CROSS C E, REDDY K A, HASEGAWA G K, CHIU H M, TYLER W S, OMAYE S T, Paraquat toxicity: Effects of selenium deficiency and anti-inflammatory drug pretreatments. In: Biochemical Mechanisms of Paraquat Toxicity. Autor Anne P., (ed). New York, Academic Press 1977. 209-211

- 59 CHOW C K, TAPPEL A L, An enzymic protective mechanism against lipid peroxidation damage to lungs of ozone-exposed rats. Lipids 1972; 7 : 518
- 60 HOWARD J K, Human erythrocyte glutathione reductase and glucose 6-phosphate dehydrogenase activities in normal subjects and in persons exposed to lead. Clin Sci Mol Med 1974; 47 : 515-520
- 60a CALABRESE E J, MOORE G S, HO S, Low glucose 6-phosphate dehydrogenase activity and increased sensitivity to paraquat toxicity. Bull Environ Contam Toxicol 1980; 24 : 369-373
- 61 ROSE M S, SMITH L L, WYATT I, The relevance of pentose phosphate pathway stimulation in rat lung to the mechanism of paraquat toxicity. Biochem Pharmacol 1976; 25 : 1763-1767
- 61a BASSETT D J P, FISHER A B, Stimulation of the pentose cycle by paraquat in isolated perfused rat lungs. Physiologist 1979; 19 : 117
- 62 WITSCHI H, HIRAI K-I, COTE M G, Primary events in lung following exposure to toxic chemicals. In: Biochemical Mechanisms of Paraquat Toxicity Autor Anne P, (ed). New York Academic Press, 1977. 1-20
- 63 WITSCHI H, KACEW S, HIRAI K-I, COTE M G, In vivo oxidation of reduced nicotinamide adenine dinucleotide phosphate by paraquat and diquat in rat lung. Chem Biol Interact 1977; 19 : 143-160
- 64 WAKIL S J, Lipid metabolism. Ann Rev Biochem 1962; 31 : 369-406
- 65 MACKLIN C C, The pulmonary alveolar mucoid film and the pneumocytes. Lancet 1954; 266 : 1099-1104
- 66 NISHIKI K, JAMIESON D, OSHINO N, CHANCE B, Oxygen toxicity in the perfused rat liver and lung under hyperbolic conditions. Biochem J 1976; 160 : 343-355

- 67 FISHER H K, CLEMENTS J A, TIERNEY D F, Early pulmonary effects of paraquat in rats. Clin Res 1970; 18 : 190
- 68 AYERS L, TIERNEY D F, Pentose pathway: A possible metabolic mechanism to protect the lung from a high oxygen tension. Amer Rev Resp Dis 1971; 103 : 906
- 69 AYERS L, TIERNEY D F, High oxygen tension and the pentose phosphate pathway in rat lungs. Clin Res 1971; 19 : 190
- 70 SMITH L L, ROSE M S, Biochemical changes in lungs exposed to paraquat In: Biochemical Mechanisms of Paraquat Toxicity. Autor Anne P, (ed). New York, Academic Press, 1977. 187-200
- 71 VIJAYARATNAM G S, CORRIN B, Experimental paraquat poisoning: A histological and electron-optical study of the changes in the lung. J Pathol 1971; 103 : 123-129
- 72 SMITH L L, ROSE M S, A comparison of the effects of paraquat and diquat on the water content of rat lung and the incorporation of thymidine into lung DNA. Toxicol 1977; 8 : 223-230
- 73 HEATH D, SMITH P, The pathology of the lung in paraquat poisoning. In: Biochemical Mechanisms of Paraquat Toxicity. Autor, Anne P. (ed). New York, Academic Press, 1977. 39-56.
- 74 REBELLO G, MASON J K, Pulmonary histological appearances in fatal paraquat poisoning. Histopathol 1978; 2 : 53-66
- 75 SMITH P, HEATH D, KAY J M, The pathogenesis and structure of paraquat-induced pulmonary fibrosis in rats. J Pathol 1974; 114 : 57-67
- 76 CARSON D J L, CARSON E D, The increasing use of paraquat as a suicidal agent. Forens Sci 1976; 7 : 151-160
- 77 GERVAIS P, DIAMANT-BERGER O, BESCOL-LIVERSAC J, GUILLAUME C, GUYON F, Problemes medico-legaux et medico-sociaux de l'intoxication aigüe par les herbicides du groupe du paraquat. Arch Mal Prof Med Trav 1975; 36 : 19-36

- 78 CASTLEMAN B, MCNEELY B V, (eds), Case records of the Massachusetts General Hospital; Case 7 - 1969. New England J Med 1967; 276 : 401-403
- 79 MCDONAGH B J, MARTIN J, Paraquat poisoning in children. Arch Dis Child 1970; 45 : 425-427
- 80 MALONE J D G, CARMODY M, KEOGH B, O'DWYER W F, Paraquat poisoning: A review of nineteen cases. J. Irish Med Ass 1971; 64 : 59-68
- 81 OREOPoulos D G, SOYANNWO M A O, SINNIAK R, FENTON S S A, McGEOWN M, BRUCE J H, Acute renal failure in cases of paraquat poisoning. Brit Med J. 1968; i : 749-750
- 82 FENNELL J J, FITZGERALD M X, FITZGERALD O, Recovery from severe paraquat poisoning following forced diuresis and immunosuppressive therapy. J. Irish Med Ass 1971; 64 : 69-71
- 83 GRABENSEE B, VELTMANN G, MURTZ R, BORCHARD F, Poisoning by paraquat. Dtsch Med Wochenschr 1971; 96 : 498-506.
- 84 NAGI A H, Paraquat and adrenal cortical necrosis. Brit Med J 1970; 2 : 669
- 85 YONEYAMA M, KAINUMA T, TAKEUCHI I, Swift death by poisoning caused by the new herbicide Gramoxone. Nihon Iji Shimpo 1969; No 2374 : 32-34
- 86 FITZGERALD G R, BARNIVILLE G, FITZPATRICK P, EDWARDS A, SILKE B, CARMODY M, O'DWYER W F, Adrenal abnormalities in paraquat poisoning. Irish J Med Sci 1977; 146 : 421-423
- 87 NIENHAUS H, EHRENFIELD M, Pathogenesis of lung disease in paraquat poisoning. Beitr Pathol 1971; 142 : 244-267

APPENDIX 1.1

Products Containing Paraquat

Paraquat is sold in 130 countries in various formulations. It is most widely sold under the trade name 'Gramoxone' but may be encountered under any of the following names:—

'Dextrone X' (U.K. 200 g/l.)	'Para-Col' (Malaysia, Indonesia. 200 g/l. Also contains diuron)
'Dexuron' (U.K. 100 g/l. Also contains diuron)	'Pathclear' (U.K. Granules 25 g/kg. Also contains diquat and simazine)
'Duanti' (W. Germany. Granules 25 g/kg. Also contains diquat)	'Priglone' (France. 120 g/l. Also contains diquat)
'Esgram' (U.K. 200 g/l.)	'Spray-seed' (Australia. 100 g/l. Also contains diquat)
'Gramonol' (100 g/l. Also contains monolinuron)	'Terraklene' (100 g/l. Also contains simazine)
'Gramoxone' (200 g/l.)	'Tota-Col' (100 g/l. Also contains diuron)
'Gramoxone' Plus (Italy. 100 g/l.)	'Weedol' (Granules. 25 g/kg. Also contains diquat)
'Gramoxone' S (200 g/l.)	'Weedrite' (Canada. Granules 25 g/kg. Also contains diquat)
'Gramoxone' ZU (Belgium, Holland. 200 g/l.)	'Weedrite' Aerosol (Canada. 0.44% paraquat)
'Gramuron' (South Africa, Mauritius. 100 g/l. Also contains diuron)	
'Ortho' paraquat (U.S.A. 2 lb/U.S. gal.)	

Since this table was compiled Shell Chemicals Ltd have introduced (1981):-

'Cleansweep' (U.K. 100 g/l. Also contains diquat)

SECTION 2

THE OCCUPATIONAL USE OF PARAQUAT

AND ASSOCIATED RISKS

2. THE OCCUPATIONAL USE OF PARAQUAT AND ASSOCIATED RISKS ¹

2.1. PATTERNS OF USE AND EXPOSURE

The bipyridyl herbicides are generally available in two forms of commercial preparation, solid (granular) and liquid. The granular formulations* are prepared for the retail market mainly in the UK and are for use in domestic gardens and similar situations. Although of some importance as agents in self-poisoning (see Section 3), they have not been incriminated as posing any hazard in use. The liquid concentrates of paraquat are available only for agricultural or commercial horticultural use and the poisons register should be signed before sale. This is not the case in many other countries, however, and such agricultural concentrates are often widely available to the general public. In the UK, the most widely used is 'Gramoxone' (ICI Ltd), a 20% aqueous formulation of paraquat ion (200 g/l) with various adjuvants such as surfactants. (The equivalent formulation under the trade name 'Dextrone' is available only to local authorities and other official bodies). There is also a variety of other combination formulations (with diuron etc.) in which the paraquat ion is at a strength of 100 g/l. Outside the UK, the ICI Ltd formulations are sold under a number of other trade names in addition to 'Gramoxone' and there is also a large number of 'pirated' formulations made in Taiwan, selling particularly in the Far East.

* Those commercially available in UK are: 'Weedol' (ICI Ltd.) formulated in sachets containing 1.5 g paraquat ion and 1.5 g diquat ion and 'Pathclear' as sachets containing 1.5 g paraquat ion, 1.5 g diquat ion and the residual herbicide simazine.

The manufacturers recommend a range of dilution for application according to the specific task to be undertaken. The highest concentration obtainable from this range of dilutions is 0.5% paraquat ion in the final spray solution, obtained by diluting 4 pints of 'Gramoxone' in 20 gallons of water. The normal rate of application, however, is considerably less than this, usually in the order of 0.1 to 0.15% paraquat ion, and frequently it may be as low as 0.05% ion in the final spray. Application is either by tractor-mounted boom sprayers (most commonly in UK) or by hand-held spraying lance with hand pump operated knapsack containers (figs. 2.1 and 2.2). Hand held lances are fitted with a variety of nozzles, usually of the flood-jet or 'polijet' type. In some tropical areas (notably Malaysia which has a high volume usage of paraquat) a number of spraymen will use hand-held spraying lances attached by flexible hoses to a tractor mounted feed tank (fig 2.3). This practice allows a much greater area to be sprayed without the necessity of frequent recharging of knapsack reservoirs. Because a single mix will provide sufficient spray solution for at least one full session of spraying, this system is intrinsically safer than standard knapsack methods, but for a variety of reasons it has only a limited application to particular terrains and land usage.

The diluted paraquat is sprayed downwards directly onto foliage. The manufacturers have listed, on the package labels, a series of operating instructions and necessary precautions to ensure safe handling, of both concentrate and spray solution. In the UK these precautions are produced after agreement with the

FIG 2.1: TRACTOR-MOUNTED BOOM SPRAYING



Photo: courtesy ICI Ltd, Plant Protection Division

FIG 2.2: HAND SPRAYING WITH KNAPSACK CONTAINERS



Photo: courtesy ICI Ltd, Plant Protection Division

FIG. 2.3: HAND SPRAYING WITH TRACTOR-MOUNTED FEED TANK



Photo: the author

Ministry of Agriculture Pesticide Safety Precautions Scheme (PSPS).

These are set out in table 2.1. Similar controls exist in many other countries. The use of mist blowers and the aerial spraying of paraquat are not sanctioned in the UK.

The manufacturer's recommendations for safe use in the UK do not include any special protective clothing for the actual spraying operation other than a face shield. Rubber gloves and a face shield are recommended when handling the concentrate. Most spray workers, however, do wear rubber boots when spraying and also frequently rubber gloves in addition.

In such spraying operations, the problem that has to be quantified is not the intrinsic hazard of the material, but the degree of risk with which its use may be associated. Considering this on a world scale, skin rashes, eye damage and other local effects are not uncommon and there is a possibility that systemic absorption could occur, either through oral ingestion, percutaneous absorption or inhalation. The published literature relating to these matters will be reviewed and then an account given of the author's investigations of risk in three separate occupational risk situations.

TABLE 2.1: MANUFACTURER'S LABEL INSTRUCTIONS FOR SAFE HANDLING OF 'GRAMOXONE'

Paraquat can kill if swallowed. Do not put in a food or drinks container. Keep out of reach of children.

Directions for use

Application: Apply through a field crop sprayer, in good condition, using a pressure of at least 2 bars (or 30 psi) or through a low pressure spraying device. When using hand held sprayers do not use in concentrations greater than one volume 'Gramoxone' 100 to forty volumes of water. Do not apply 'Gramoxone' from the air, or by means of a mistblower or fogging machine.

Avoid spray drift: Do not spray in windy conditions.

Precautions

The Poisons Act 1972, available from HMSO, applies to this product.

Wear protective gloves and face shield when handling the concentrate.

Wear face shield when handling and applying the diluted formulation.

Take off immediately heavily contaminated clothing and wash underlying skin. Wash clothes before re-use.

When using do not eat, drink or smoke.

Wash splashes from skin or eyes immediately.

Do not breathe spray mist.

Wash hands and exposed skin before meals and after work.

2.2. LOCAL TOXIC EFFECTS

A variety of local effects on eyes, mucous membranes, skin and nails have been recorded. The degree and extent of these lesions depend on the duration of contact with paraquat and the extent of the dilution of the material. These reactions derive from the delayed caustic effect of paraquat and prompt first aid measures are usually effective in preventing the development of any severe tissue response.

2.2.1. CUTANEOUS EFFECTS

Paraquat acts as a delayed caustic and the effects are made worse both by occlusion and by the surfactants and other adjuvants in the commercial formulations. Animal experiments have resulted in a range of effects from mild reddening to superficial epidermal sloughing^{2,3}. Reddening is usually associated with the development of some hyperkeratosis followed by desquamation as the lesion heals. This is the response most usually seen in agricultural workers and others who have received either concentrate burns or have been exposed to spray for long periods. In general the burns are superficial and are thus in contrast to concentrated acid and alkali burns. Occasionally bullae have developed after skin damage from the agricultural concentrate⁴.

The incidence of skin reactions appears to be relatively high with hand held equipment, especially in workers engaged in extensive or long term

spraying programmes. One study suggested that up to half the population of spray operators could develop skin responses to paraquat, chiefly through prolonged contact with spray solutions⁵. Other workers have reported much lower incidences of skin problems^{6,7}. Apart from the expected involvement of hands and arms, the groin and genitals are frequently affected, either as a result of spillages⁸ or through the use of leaking spray apparatus. The spray solution may leak under pressure from poorly maintained knapsack reservoirs and run down the man's back to set up irritation in the groin area as a result of clothing being soaked. Such problems may be overcome by improving the maintenance of equipment and by the use of simple but efficient protective clothing (fig 2.4). In the writer's experience, the use of a plastic bag as illustrated has reduced the incidence of groin rashes to almost nil on tropical estates.



The presence of skin abrasions frequently worsens the local effects of paraquat. Such effects are more often seen in the tropics where sprayers may work barefooted, although a case has been reported from the UK of a man spraying paraquat with no protection for his legs which were scratched by goose grass (Gallium aparine L) resulting in a vesicular lesion developing on them⁹. Such dermal effects may be avoided altogether by observing the simple precautionary measures laid down on the label, including the rapid washing of concentrate spills from the hands and the appropriate changing and laundering of working clothes. The



rapid removal of sprayer from the ground would also prevent the sort of accident reported by Relyea and Martin.¹⁰ In such a case no fluid protection is available.

FIG. 2.4: PLASTIC BAG WORN AS SIMPLE PROTECTION BY MALAYSIAN SPRAY MAN



Photo: the author

rapid removal of spillages from the ground would also prevent the sort of accident reported by McDonagh and Martin ¹⁰ in which a child was found playing with a pool of spilled 'Gramoxone' and which resulted in a large first degree burn of the thigh and an erythematous rash of the hands taking some four weeks to clear with conservative treatment. The relationship between dermal contamination and possible systemic intoxication is discussed below (Section 2.3.3).

A phenomenon related to the dermal effects of paraquat is the occurrence of delayed healing. This has been observed by the author among spray workers, particularly in the tropics where legs and arms may be unprotected and superficial lacerations from vegetation such as thorns are accordingly common. It has also been observed among formulation workers studied by the author, both in the UK and in Malaysia ⁴. The phenomenon manifests itself as a failure of small lacerations and abrasions to heal spontaneously in the usual time. Small wounds tend to remain open for several days with an increased risk of infection. The condition in some cases appears to reflect a lack of personal hygiene, but this is not true of all cases.

2.2.2. EPISTAXIS

Nose bleeds are a relatively infrequent complication of both paraquat spraying and formulation. In the author's experience, this rarely occurs as frank bleeding and the common

complaint is one of spotting of the handkerchief after blowing the nose. In formulating plants the problem is most frequently encountered among those working with solid formulations which inevitably give rise to some fine dust which impinges on the nasal mucosa. The phenomenon is usually encountered in the first week or so of working and thereafter the incidence of epistaxis falls rapidly⁴. The effect appears to be the result of the direct irritant/caustic action of paraquat on the nasal mucous membrane resulting in small superficial erosions with capillary bleeding.

Epistaxis is relatively uncommon among spray operators under normal circumstances, although it may occur when spraying is conducted against the wind or when the operator works in the spray mist⁵. Neither situation is to be considered good spraying practice. The use of mist blowers for applying paraquat has resulted in severe nose bleeding, although symptoms have cleared following cessation of exposure¹¹. Again, it is worth noting that although frequently used, particularly in Australia, the manufacturers do not recommend the use of this equipment.

2.2.3. NAIL DAMAGE

Nail damage as a result of exposure to paraquat was first reported by Samman and Johnson in 1969¹². They described three cases all of which were due to the repeated gross contamination of the hands with agricultural concentrate as a result of careless handling. Although in one case damage was

considerable, in all cases there was eventually complete and normal regrowth of the nail. Similar cases among agricultural workers have been reported by others^{13, 14} but the most extensive study of this problem was by Hearn and Keir⁷ on the Trinidad sugar estates, who reported 55 cases of nail damage as a result of contamination with dilute spray material rather than concentrate.

The workers on the estates all used standard Saval knapsack sprayers with 'flood-jet' nozzles and the final spray strength solution never exceeded 0.02% (1:100 dilution of the 20% concentrate). The earliest lesions to develop consisted of a localized white or yellow discolouration at the base of the finger nail together with a number of transverse white bands on the more commonly affected nails. The nails of the index, middle and ring fingers of the right hand were those most commonly involved, as a result of leakage of dilute paraquat from the junction of the flexible hose and the hand-held lance. Nail deformity, in some cases, developed to a progressive loss of nail surface, leading to deformation and eventual shedding of the nail plate. As in other studies, regrowth of the nails was normal in all cases once further contamination had been prevented.

The mechanism by which nail damage is produced is obscure, although it has been suggested¹² that infection may play a major role. Similar lesions have been observed by the author in those working in formulating plants, handling both solid and liquid formulations of paraquat⁴.

2.2.4. EYE INJURY

There have been numerous reports of eye injury following splashes or other accidental contamination with paraquat ¹⁵⁻²¹. Although damage may be severe, in general it is only superficial and responds well to therapy. Experimental work with rabbits has shown that the instillation of paraquat into the conjunctival sac is followed after 12 to 14 hours by a severe inflammatory response ². This effect has been shown to be dose-related with a range of effect from severe conjunctivitis and occasional slight corneal damage (at strengths from 6.25 to 12.5%) to congestion and swelling of the iris, corneal opacification and the development of a pannus reaction (at 25 to 50%) ²². A typical response showed gross conjunctival injection, with swelling and partially closed lids, a mucopurulent discharge and diffuse corneal opacification. Similar responses are found following human eye contamination with concentrated paraquat solutions. It is likely that the formulating materials play a part in the development of the reaction, as they may be irritant in their own right or potentiate the effects of paraquat.

In the majority of reported cases, recovery has been complete within 24 to 48 hours following injury. Treatment consists of prolonged eye irrigation with water or a buffer solution followed by the topical use of steroids (hydrocortisone) and antibiotics (usually oxytetracycline or neomycin). It has been shown that adequate control of infection and the prevention of adhesions between the denuded bulbar and

palpebral surfaces are the mainstays of treatment²³.

Complications have been reported and in one case¹⁵ the onset of eye damage was insidious and not fully apparent until a week after the incident in which a paraquat/diquat mixture had been splashed into the eye*. Damage was extensive with severe keratitis in spite of initial irrigation and atropine was required to control uveitis. Joyce¹⁶ has reported one case in which natural healing was never complete. At four weeks after initial damage there remained a large corneal opacity surrounded by areas of keratitis. This corneal damage was still present five months after exposure and required surgical intervention.

Although with rapid treatment, the evolution of most cases of paraquat eye injury follows a benign course resulting in full healing and a restoration of normal function, it should be remembered that delay in treatment may result in permanent damage. That is why the use of a face shield is recommended whenever the agricultural concentrates are handled. It is unlikely that diluted spray solutions would cause actual eye damage, transient irritation being the usual feature after such material has got into the eye. Nonetheless, in the UK, the PSPS requires the recommendation for the use of a face shield when spraying to be added to label precautions (see table 2.1).

* This mixture ('Preglone' Extra, ICI Ltd.) is now no longer on the market.

2.3. SYSTEMIC TOXICITY FROM USE

2.3.1. GENERAL OBSERVATIONS

There appear to be no adequately documented cases in the world literature of serious systemic absorption of paraquat leading to recognisable toxic effects as a result of proper occupational use of paraquat and with adherence to the recommended precautions. Nonetheless, there have been a number of claims that such poisoning may occur in the course of ordinary usage.

Fitzgerald and his colleagues²⁴ for example, made a detailed study of 13 cases of paraquat poisoning following agricultural use, of which six were fatal. Although it seems likely that all but one of the fatalities in this series arose from ingestion of the concentrate rather than absorption during the course of work, Fitzgerald makes a valid point that there is a widespread tendency among spray workers, and farmers generally, to ignore even elementary safety precautions and it is not realistic to expect workers to maintain consistently high standards of care and avoid carelessness or stupidity without adequate supervision.

An extensive survey of the health hazards associated with paraquat spraying was commissioned by the California Department of Food and Agriculture in the United States²⁵. In this document Peoples and his co-workers concluded that paraquat was responsible for between 25 and 40 reported occupational illnesses each year in the period 1965-1976.

The document, however, relied on poorly investigated anecdotal evidence and much of the interpretation of signs and symptoms is confused and is misleading to such an extent that suicidal deaths are reported as deaths 'from exposure'. Nonetheless, in noting the cases of fatal accidental ingestion of paraquat formulations, the necessity for adequate supervision and proper storage is underlined once again. The poor quality of the anecdotal evidence that prompts support for stricter control of paraquat, may be illustrated by the following case reports (quoted from Peoples et al²⁵):

1. A gardener was sprayed on the face and arms with paraquat when the hose on a power sprayer separated from the nozzle. He experienced fingertip paresthesias and light-headedness. The diagnosis was inhalation of paraquat spray. Treatment was provided.
2. When driving a weed sprayer in almonds, a worker inhaled paraquat spray. He experienced a tightness and pain in his chest. Some safety equipment was used, but no face protection. A training record indicated that this man was knowledgeable of safety procedures. Inhalation of paraquat was the diagnosis, and 10 cc calcium gluconate I.V was the major treatment provided.
3. An employee was mixing and loading paraquat when a line developed a leak, spraying him in the face with the dilute mixture for 10 to 15 seconds. He then went to a stream of water and washed. The man subsequently became dizzy, nauseated and vomited prior to going to a hospital. He was hospitalized and given the following tests: X-ray; routine blood sampling; EKG; and was treated with intravenous fluids. He missed more than five days of work.
4. While spraying for weeds with a hand sprayer, a worker walked back through the sprayed area. He developed abdominal cramping, diarrhea, and blurred vision. Gloves were the only protective gear worn. He was examined by a physician and conducted the following tests: chest X-rays; CBC; BUN; serum creatinine; electrolytes; liver function; serum alkaline phosphatase; serum bilirubin; and serum trypsin levels. Treatment was administered.

In these and the many others quoted in this report no attempts are made to reach an adequate diagnosis and most, apart from skin and eye effects from direct contact, are examples of what the writer has referred to elsewhere as the 'paraquat fear syndrome'⁴ on the one hand, associated with a considerable degree of ignorance of the toxicity of paraquat and its resultant clinical effects on the other. The symptoms and signs described do not relate to what is known of the effects of paraquat poisoning, although it is possible that some of the effects described might have been the result of exposure to insecticides. That the authors of this report were unable to distinguish between two very different types of symptom pattern is almost inconceivable.

Other literature reports of illness have implicated paraquat poisoning in respect of occupational exposure as the cause, but data are clearly insufficient either to support or deny such a causal relationship between exposure and alleged effect. A good example of this is to be seen in the case reported by Mourin²⁶ in which a peripheral facial palsy was initially attributed to paraquat exposure, although later shown to be much more likely the result of previous geniculate herpes zoster²⁷. Another example where cause and effect had little to do with paraquat was reported from Italy²⁸. The history was one of chronic hepatitis in a man with heavy wine consumption and extensive exposure to the known hepato-toxic chlorinated hydrocarbons. Nonetheless, the causative agent was considered to be paraquat as he had used this pesticide for spraying (for the first time) a few days before symptoms began.

Under certain conditions, however, systemic poisoning may occur, either by oral ingestion or dermal absorption.

2.3.2 ORAL INGESTION

The oral ingestion of paraquat is only likely to occur in occupational use under the following sets of circumstances.

It may occur accidentally, when concentrates such as 'Gramoxone' have been decanted into unlabelled containers, against label instructions and good agricultural practice.

The great majority of accidental poisonings have resulted from such malpractice and it is potentially the greatest risk from paraquat. Fortunately, an awareness of the dangers has markedly reduced this problem in Great Britain so that in the past few years cases of accidental poisoning have numbered only one or two per annum.

The following case, investigated by the author, illustrates the type of circumstance which may occur and the tragic results which frequently follow:

A 47-year old male farm worker was engaged in spraying paraquat using a tractor-mounted spray.

In order to facilitate mixing in the field he carried two unlabelled containers mounted on the tractor bumper, one containing the 20% agricultural concentrate of paraquat and the other water.

During the course of his work he became thirsty and drank from one of the containers, thinking it held

water. Unfortunately it was the one containing paraquat. Although he spat out what was in his mouth, he had already swallowed sufficient to produce toxic effects and in spite of early medical treatment he died two weeks later from respiratory complications.

Accidental ingestion may also occur when operators suck or blow out blocked pipes or nozzles of spray apparatus. This practice is usually associated with tractor-mounted rather than hand held equipment and in most cases results only in the ingestion of dilute paraquat which, at recommended application rates, is most unlikely to be lethal or even to produce serious symptoms. The report of such an occurrence during spraying operations in Israel²⁹ however, suggests that even with dilute material some systemic toxicity may occur. In this case a 30-year old healthy male was accidentally sprayed in the face, as a result of which dilute paraquat went into his mouth and was swallowed. The authors reported minor and transient changes of renal and pulmonary function with an uneventful recovery following renal dialysis. Such practices, however, should be strongly discouraged even though it may be estimated that the lethal amount of diluted paraquat would be in the order of two litres at a standard dilution of 0.1% (1:200 dilution of 'Gramoxone'), assuming the fatal adult human dose to be in the order of 2 to 3 g³⁰.

Oral ingestion may also occur as a result of swallowing the 'run off' caused by droplets impinging on the face should the operator work in the spray mist. Such a practice contravenes

the label instructions, but occasionally occurs. At recommended spray strengths of not more than 0.5% paraquat ion (1:40 dilution of the standard 20% concentrate) it would seem to be impossible to ingest sufficient paraquat in this way to produce symptoms of poisoning, although this has been claimed by Malone and his colleagues ³¹, who erroneously refer to the inhalation of droplets. At higher concentrations of spray solution and under adverse conditions, such as spraying into the wind, local caustic effects from oral contamination have been reported from Eire ²⁴. Even in these circumstances there is no clear evidence that systemic effects resulted from these conditions alone. Repeated exposure of this nature, although likely to produce local skin effects, would still not produce systemic intoxication. The 'no effect' level for paraquat on dogs, generally the most sensitive species, is quoted by the FAO ³² as 50 ppm in the diet over a two year period. This represents a daily intake in the order of 90 to 100 mg for an adult man, equivalent to 90 ml of spray solution at dilutions of 0.1% paraquat ion.

2.3.3. DERMAL ABSORPTION

Skin contamination is always a risk in field operations with any pesticide. The problem is greater in countries where high ambient temperatures and humidity preclude the extensive use of protective clothing. Paraquat, being a caustic material, has local irritant effects, but it is relatively poorly absorbed through intact skin, particularly at spray strengths ^{2, 3}.

Mention has already been made in respect of local toxic effects seen in the two trials conducted on Malaysian rubber estates reported by Swan⁵. The operators used spray dilutions of 0.05% paraquat (equivalent to 1:400 dilution of 'Gramoxone') and conditions were such that the spray workers were exposed to significant quantities of paraquat ion, demonstrated by the fact that paraquat could be detected in the urine of all the spraymen at some stage of the trial. Under these circumstances, although local effects on skin did occur, as noted earlier, there were no systemic symptoms nor signs, and chest radiographs were normal. Swan was also able to demonstrate that attention to personal hygiene was sufficient to prevent risk from dermal absorption.

These results were largely confirmed by Hearn and Keir⁷ who demonstrated the development of local skin and nail effects in workers on Trinidad sugar estates, but found no evidence of systemic absorption. These workers were using higher spray concentrations than those in the Malaysian trial. The dilutions of the 20% concentrate were from 1:100 to 1:200 (i.e. from 0.2 to 0.1% paraquat ion in the final spray solution). Similar results have been recorded in the author's studies of formulation and long-term spray workers, some of which have been published^{4, 6}. They will be reported in detail under Section 2.4, but at this stage it should be recorded that these workers showed no evidence of any systemic effects from exposure to paraquat.

McElligott³ has shown that, to some extent at least, the degree of percutaneous absorption of paraquat is a function of concentration and with proper use exposure will only be to low concentrations in the spray solutions. At the usual spray dilution of 0.1% paraquat ion, for example, and assuming that the lowest published dermal LD₅₀ for paraquat of 80 mg/kg is applicable³³, it would require the absorption of all the paraquat contained in 2 litres of spray solution to produce a fatal outcome. In fact, Staiff and his colleagues³⁴ have shown that the likely dermal dose for a spray operator using the recommended rates of application would not exceed 3 mg/hour, that is a total dose of 24 mg per day, assuming an eight hour working day. Such an exposure represents a dose of approximately 0.4 mg/kg, or no more than 0.5% of the lowest estimate of the dermal LD₅₀ per day. This particular study was designed to determine the potential exposure, both dermal and respiratory, of field operators using conventional low pressure power spray equipment at spray strength of 0.15% paraquat ion.

Further evidence for the low level of risk from skin absorption comes from the work of Hogarty and his team³⁵ as part of a large study to determine the particle size analysis of drops produced by normal agricultural spray nozzles, the concentrations of paraquat likely to occur in the air breathed by a spray operator and the exposure of spray operators under actual working conditions. Exposure pads of lint gauze, approximately 6.25 cm² in size, were placed on the neck (open to the air) on the back of the wrist (beneath clothing) and on the groin

(beneath clothing). These operators sprayed a total of 4.84 kg paraquat ion over 9 days at dilutions of 1:40 and 1:80 (i.e. 0.5% and 0.25% paraquat ion). Only two out of 87 analyses showed paraquat (one from a neck pad and the other from the wrist of two separate operators on two separate days). The amounts were minute (5 µg per pad: detection limit 5 µg), indicating that the risk associated with skin contamination with proper spraying procedures is negligible. It must be noted, however, that this trial was carefully supervised and a greater level of contamination would be expected under normal spraying conditions in the field. This was the case in field studies undertaken by a team for which the author was responsible and which will be discussed later (Section 2.4.2).

Although not entirely relevant to the problem of paraquat, it is worth noting that a study was undertaken in man of the percutaneous absorption of the very closely related bipyridyl, diquat³⁶. A single dose of 4 g of ¹⁴C-labelled diquat in aqueous solution was applied to the exterior surface of the forearm of six healthy male volunteers. The material was left for a period of 24 hours and the extent of percutaneous absorption in this time was estimated from the amount of diquat excreted in the urine (recovered as ¹⁴C) over a period of five days, since diquat is rapidly excreted in the urine and not retained in the body. The mean value of the total excretion amounted to only 0.3% of the original radio-active dose, half of that amount being recovered in the first 24 hours. This type of study is open to criticism, not least in respect of the very small

doses used, but is is nonetheless reasonable to accept the author's conclusion that diquat is only poorly absorbed through intact skin, confirming the results of animal experiments on the bipyridyl family^{2, 3}.

Nonetheless, two well-documented cases have been reported in which occupational exposure resulted in death from percutaneous absorption. The first was reported by Jaroš³⁷ from Czechoslovakia, and it is clear that in this case the circumstances were very far from normal spraying practice. The spray was applied at a dilution of 1:4 (equivalent to 5.0% paraquat ion), which is ten times the highest recommended rate and at a concentration which will produce caustic burns of the skin, facilitating absorption. Furthermore, the knapsack sprayer itself leaked and allowed the solution to run down the man's back throughout the spraying operation. In spite of the skin damage the man did not report for any medical attention until six days later, by which time irreversible pathological changes had occurred. The circumstances of this case could be viewed as an example of paraquat gross misuse.

The other case was reported by Levin and his co-workers³⁸ and was again associated with the use of high spray concentrations. According to Levin et al the spray concentration was 2.8% paraquat ion, but independent information (E. Bougas, 1979 personal communication) would suggest that Levin's figure derives from a miscalculation and

the actual spray strength was in the order of 3.5% paraquat ion. There is also some conflict about the type of spraying apparatus used. According to Levin, the sprayer used was a 'Herbi' type applicator, using gravity and an electrically powered spinning disc to distribute the spray. Privately obtained information suggests that the 'Herbi' applicator had been modified to take a knapsack reservoir and the junction between the reservoir and the applicator had a serious leak. In point of fact, the issue is not at stake in either case, since neither are recommended methods of applying paraquat, although the makeshift type of apparatus the author has been given to understand was actually used represented a significantly greater risk to the operator. Furthermore, additional information would indicate that the operator was using a mixture of 1 litre of 'Gramoxone', 1 litre of 'Reglone' (diquat formulation) in 2 litres of oil and 2 litres of water. This represents a 1:6 dilution (3.3%) of paraquat and a similar dilution of diquat, so that the total bipyridyl ionic strength was above 6 per cent.

In view of this evidence of gross malpractice, it is not altogether surprising that lengthy spraying operations were followed by a tragic outcome, and while some of Levin's results and conclusions are open to question, the real issue hinges upon the proper use of an agricultural spray according to the manufacturer's recommendations.

Three other cases of possible occupationally related fatalities have been recorded, but the details are not sufficiently clear to be certain of the route of absorption.

Fitzgerald and his co-workers²⁴ report a case in which a 50-year old farmer died following use of a leaking spray for a full day of spraying. There is a possible link in this case with the fact that the man apparently suffered from extensive dermatitis which could have facilitated the absorption of paraquat through the damaged skin. There is no information on the spray strength used. Newhouse et al³⁹ reported a case in Canada where a woman sprayer allegedly died following the spraying of paraquat. This case has so many question marks over it that reaching a final conclusion is almost impossible. It should be noted, however, that the pathological process was very prolonged (end of August to middle of October) and all other documented cases of fatal dermal absorption indicate a relatively short time between exposure and death. Furthermore, the degree of organ involvement described (lung, liver and kidney) is not consistent either with a lengthy absorption of a lethal dose or a short absorption of a 'just lethal' dose. Such organ involvement is usually associated with a single large exposure and in most cases following oral ingestion. This case would suggest that, while there is some circumstantial evidence to suggest that the woman's death was related to exposure to paraquat, for this to have been the result of dermal absorption would indicate a degree of massive exposure that does not seem to have been present and one is left with the possibility that there may have been some (possibly deliberate) oral ingestion.

The third case is of another woman whose death initially appeared to be due to occupational exposure, but which

subsequent investigation suggested was not directly related to the application of the hericide. A woman who was involved in spraying was reported by Weston and Dixon⁴⁰ to have had extensive contamination of her arms and hands. Additionally she was stated to have 'accidentally' swallowed some material while spraying. It was, thus, not initially clear as to whether the case was one of oral or dermal absorption. However, the author makes the important point that the deceased woman was a chronic alcoholic who tasted various unknown liquids in order to discover whether they contained alcohol. At the time of consuming the herbicide, the evidence suggested that she was intoxicated and thus death in this case must be viewed as a result of 'accidental ingestion' rather than from any other cause, and certainly it was not primarily related to occupational exposure.

It is worth noting two other cases of fatal skin absorption of paraquat, although neither are related to occupational exposure. Both^{41, 42} involved the prolonged application of the 20 per cent agricultural concentrate directly to the skin, including the sensitive area of the scrotum, in order to 'control' body lice. Such misguided 'therapeutic' applications can in no way be compared to the situations that arise in normal agricultural practice.

In one case⁴¹ the patient presented with extensive genital corrosion and ulceration which was initially claimed by the patient to have occurred following an accidental spillage of paraquat concentrate at the time of a weed spraying operation

three days before. Fortunately, the authors of the report had doubts as to the reliability of this history and further questioning elicited the true facts. The patient 'revealed that he had intentionally applied the chemical to his under-wear so that it would remain in close contact with the genitalia as a treatment against phthirus which he claimed to have had at the time'. He died following the development of respiratory complications.

The other case⁴² was very similar. Here a man applied the concentrate to his beard and scalp to rid himself of lice. A friend had advised him that 'the medicine (paraquat) was very good for killing insects'. Three days later he was admitted to hospital with his face and scalp covered with infected sores and blisters. He died six days after he had applied the paraquat to his skin.

On the other hand, that a fatal outcome following extensive skin contamination is not inevitable, is illustrated by a case in which a small child who had played with a pool of spilled 'Gramoxone' developed extensive skin damage⁴³. Within six to eight hours after the incident, an erythematous rash with blistering developed on one thigh and both hands, but healing took place with no systemic complications. It is likely that prompt action prevented any significant percutaneous absorption.

2.3.4. INHALATION

It is not surprising, in view of the prominence of lung pathology in cases of paraquat poisoning, that concern has been

expressed about the possibility of pulmonary damage developing in spray operators exposed to paraquat. Some authors have claimed this to be a genuine risk in spraying operations, but the hard evidence is remarkably slim and, as will be discussed in detail later, technical considerations virtually rule it out as a practical possibility. Malone and his colleagues ³¹ nonetheless reported a case of a 46-year old man who was spraying paraquat in windy weather, conditions alleged to increase the risk of inhalation. About four hours after the spraying he developed symptoms of nausea and vomiting and six days later there was evidence of minor renal damage with traces of paraquat in the urine five and eight days after spraying. Serial chest X-rays were normal and recovery was uneventful. Malone believed the cause of the symptoms was inhalation of paraquat droplets and absorption through the respiratory tract, but the clinical details suggest that ingestion would be a more likely cause.

Similarly, Peoples, Maddy and Riddle ²⁵ have reported a number of cases of non-fatal and usually transient illness which they associate with 'inhalation experience'. In one case, for example, they report that a driver of a spraying rig 'inhaled' paraquat spray due to the wind blowing it into the cab. Shortly after this incident he began to develop shortness of breath and nausea. He was seen by a physician who diagnosed 'paraquat poisoning' and was given symptomatic treatment only. Symptoms subsided rapidly and he was assigned to other work. As had been indicated earlier, most of the cases described in this report experience symptoms that

bear little relation to the toxicity of paraquat, such as paraesthesia, lightheadedness, abdominal cramps, wheezing etc. It is just possible that the various formulation adjuvants could have been responsible for these symptoms, but to report these cases as 'paraquat poisoning' from inhalation can only be viewed as spurious.

Mention should be made, also, of the reports from France^{44, 45} in which cases have been reported as 'intoxication par voie respiratoire'. Conso⁴⁵ reported sixteen such cases, but the grounds for considering them to be cases of poisoning by inhalation are not at all clear. Personal discussions with Mme. F. Conso and her colleagues at the Hôpital Fernand-Widal in Paris failed to elucidate the criteria used for their classification. It would appear, however, that the cases reported were in fact of respiratory symptoms associated with paraquat spraying and without any genuine evidence of cause and effect. Indeed, the circumstances of some of these cases make respiratory uptake most unlikely, although this group of workers continue to express this possibility in spite of the wealth of evidence against it⁴⁶. Nonetheless, these cases have become incorporated into the literature on the subject as poisoning following the inhalation of paraquat.

In this regard, it is worth reporting a fatal case of pesticide poisoning which was claimed to be related to inhalation of paraquat spray, but for which other explanations are equally, if not more, applicable. The writer came to be associated with this case after the death of the patient.

The patient was a middle aged male farmworker who regularly used 'Gramoxone' and an unspecified organo-phosphate insecticide using a standard knapsack sprayer. Such a mixture is most unusual and not in fact suitable for normal use in agriculture or horticulture. The strength of the spray solution was not discovered. A few hours after spraying, the patient developed severe diarrhoea with abdominal cramps and tenesmus. There was also some nausea and vomiting together with dysuria and frequency. He was admitted to the local hospital, but no investigations were undertaken for two days, by which time the patient was markedly dyspnoeic with some cyanosis. On examination, crepitations were heard at both lung bases, and a chest X-ray showed extensive pulmonary oedema. The patient's course was steadily downhill and he died 30 days after admission in cardio-pulmonary failure. At no time were urine or blood estimations for paraquat undertaken nor estimations of erythrocyte or plasma cholinesterase in view of the involvement with organo-phosphates. The post-mortem examination included no tissue paraquat estimations, but the lungs showed 'diffuse fibro-productive interstitial pneumonitis' together with 'extensive areas of bronchiectasis and infiltration compatible with a previous history of chronic bronchitis'. The heart showed moderate right sided hypertrophy. The gastro-intestinal tract showed no evidence of ulceration and there

was only mild renal congestion and fatty infiltration of the liver.

The circumstantial evidence could incriminate paraquat as the causative agent in this man's fatal lung disease, but the case raises many questions. Of these the most important relates to the symptomatology. The acute gastro-intestinal upset is most atypical of paraquat poisoning and would in any case be unexpected if the route of entry was via the lung, since paraquat only acts on the gut as a direct irritant and there was, furthermore, no evidence of this at post-mortem.

Again, no urinary or blood estimations of paraquat were undertaken, so that there is no evidence that paraquat was actually absorbed. Indeed, the clinical picture, with abdominal cramps, nausea, vomiting, diarrhoea and subsequent pulmonary oedema is more akin to organo-phosphate poisoning than it is to paraquat intoxication. This case has been discussed in detail as a good example of the danger of jumping to conclusions on the basis of insufficient data. Although recorded as a case of occupational paraquat poisoning following inhalation of spray, the actual evidence to support this diagnosis is flimsy indeed.

Recently, two further reports have appeared^{47, 48} suggesting that inhalation of nebulised paraquat can occur under normal working conditions and give rise to pulmonary symptoms. Both reports, however, are strictly anecdotal with no supporting data and,

as will now be discussed, the weight of evidence militates against the possibility of significant paraquat inhalation in normal agricultural practice.

On the assumption that both systemic poisoning and direct lung damage can occur as the result of inhalation of paraquat in occupational use, some animal experimental work has been carried out. Several hours' exposure to concentrations of paraquat in the order of 1.0 mg/m³ in aerosols containing more than 80% by weight of droplets between 2.5 and 5.0 micron diameter produced severe bronchial irritation⁴⁹. The effects, however, were all local and it was not found possible to induce a pulmonary fibrosis by exposure to inhaled paraquat. More recently at very high exposure levels (200 mgm in 134 litre chamber over 2 hours for up to 5 exposures per week) localised lung changes were induced in rats⁵⁰, but such exposures could not be paralleled by the most extreme working conditions.

The real point at issue, however, is whether there is any real possibility of inhaling material in sufficient quantities to do damage as the result of normal spraying operations. The upper limit of respirable size (i.e. capable of penetrating to the alveoli) is now generally put at 5 microns⁵¹.

Two trials have shown that standard spraying equipment fails to produce significant levels of droplets in this respirable

range of less than 5 micron diameter. The first of these trials was a careful characterisation of the droplet spectrum of standard knapsack spray jets of the 'swirljet' and 'polijet' type to which reference has already been made³⁵. The results demonstrated that the respirable fraction produced by agricultural sprays of this type is only of the order of 0.001% of the total spray volume and even the volumetric amount of sub 16 micron droplets is very small. It was also shown that the volume of droplets actually reaching the operator's breathing area represented an insignificant fraction of the total spray volume. It was found that under static trial conditions the concentration of paraquat in the air was unlikely to exceed 50 mg/m³ and on average would be more likely to be of the order of 10 mg/m³. These conditions were slightly artificial and results obtained from field conditions would give a better picture. Under field conditions the maximum concentration of paraquat to which an operator would be exposed at recommended dilution rates was found to be in the order of 12 mg/m³. Even if as much as 50% of this amount were in the form of respirable sized droplets, it would still represent an inhalation dose incapable of producing serious effects, particularly when these figures are compared with the levels used for animal experiments quoted above. Similar results were reported by Staiff et al³⁴ in a trial using spray dilutions of 0.15% paraquat ion, although with different equipment. In neither trial was paraquat detected in the urine of the spray operators with a detection

78

limit of 0.02 ppm. Staiff in fact calculated that based on the dermal LD₅₀ of 80 mg/kg quoted by Kimbrough and Gains ³³, the combined potential dermal/respiratory exposure obtained would represent only 0.06% of a 'toxic' dose per hour of exposure. Furthermore, the maximum recorded air concentrations of 12 mg/m³ found by Hogarty ³⁵ under normal field conditions are only a fraction of the currently accepted Threshold Limit Value for airborne paraquat contamination of 100 mg/m³. It has been shown by Litchfield et al ⁵² that there is no organ accumulation of paraquat at these low levels of absorption. It may be concluded that the inhalation of droplets in normal agricultural spraying practice does not represent a significant hazard to health and inhalation of toxic chemicals is only likely to be a problem with compounds of high vapour pressure, such as organo-phosphates.

2.4. INVESTIGATIONS OF OCCUPATIONAL EXPOSURE

The foregoing survey of the available evidence in the published data would indicate, as already suggested, that the degree of risk associated with the use of paraquat in normal agricultural practice is negligible. Nonetheless, certain gaps exist in available knowledge and this is especially true in relation to long term exposure, either in formulation or in agriculture, in which special risks might arise through repeated exposure. Furthermore, as the evidence of fatalities through percutaneous absorption would indicate, there appears to be a relationship between the degree of risk and the concentration of paraquat to which an individual is exposed. This is of particular importance in view of the increasing use, especially in developing countries, of low volume-high concentration spray applicators such as the Micron 'Herbi'. Accordingly, three studies were undertaken to look at:

1. the possible problems associated with formulation;
2. the possible problems associated with long term spraying, and
3. the relative risks of high and low volume spraying techniques.

2.4.1. FORMULATION WORKERS

This study was designed to look specifically at workers with significant and continuous exposure to paraquat for several years in order to determine whether such workers developed

chronic clinical problems with particular reference to the incidence of chronic skin conditions. This work has already been published⁴.

METHODS

(a) Population

Two groups of workers involved in the formulation of paraquat based herbicides were selected for study. It is generally agreed that workers involved in the continuous manufacture and formulation of agricultural chemicals are likely to have a greater degree of exposure than those using them in the field, such as farmers and spray operators, whose exposure in temperate climates is usually intermittent, often infrequent and who also use many types of pesticides making any effects which may occur difficult to interpret. The first group of workers consisted of 18 men at the ICI Plant Protection Division formulation plant at Yalding in Kent. Eight members of the group had worked only with solid formulations of paraquat involving exposure to dust, seven had handled concentrated liquid formulations only and had been faced with problems of spillages and splashes, and three workers had been involved with both types of formulation. The mean age of the group was 44.7 years (range 22-61 years) and the working week was 37½ hours, to which may be added a variable degree of overtime, likely to be about 10 percent. The length of time from first exposure varied from 1 year, 4 months to 12 years, 6 months (mean 5 years, SD 3.0).

Partial protective clothing was worn which consisted of overalls, rubber aprons, rubber gloves, rubber boots and caps

and face shield or goggles when handling liquid formulations.

Overalls, rubber gloves, rubber boots, caps, goggles and an approved dust mask were used by those handling solid formulations.

The second group of workers also consisted of 18 males from the Chemical Company of Malaysia formulation plant at Kelang, Malaysia. This group of workers was of mixed race, mainly Malay with some Indian and Chinese, with a mean age of 29 years (range 23-39 years). They were involved only with liquid formulations of paraquat and put in a working week of 42 hours with overtime, which was again estimated at about 10 percent. The length of time from first exposure was from 6 months to 6 years 6 months (mean 2 years 4 months, SD 1.6). This group of workers also wore protective clothing of the type outlined above, but with the high ambient temperature and humidity of Malaysia, the use of goggles and rubber aprons was frequently neglected and gloves also were commonly not worn.

The details of these two groups is set out in tables 2.2. and 2.3. and the pattern of exposure in table 2.4. Unfortunately production figures are not available, but it is known that the amount of paraquat handled in the two plants per year is very considerable and may be measured in tonnes of ion.

Liquid formulations of paraquat contain either 20 or 10 percent of paraquat ion, together with a variety of wetters and stabilisers. Some formulations also contain other herbicides,

TABLE 2.2 DETAILS OF YALDING (UK) WORKFORCE

Subject	Sex	Age (years)	Ethnic group	Total period of exposure to paraquat	Length of time from first exposure to paraquat	Formulation handled
1	M	22	Cauc.	1 yr 4 mths	1 yr 4 mths	S
2	M	23	Cauc.	2 yrs	2 yrs	S
3	M	43	Cauc.	2 yrs 6 mths	2 yrs 6 mths	S
4	M	24	Cauc.	3 yrs	3 yrs	S,L
5	M	49	Cauc.	3 yrs	3 yrs	S
6	M	43	Cauc.	3 yrs	3 yrs	L
7	M	46	Cauc.	3 yrs	3 yrs	L
8	M	51	Cauc.	4 yrs	4 yrs	S
9	M	55	Cauc.	4 yrs	4 yrs	L
10	M	61	Cauc.	4 yrs	4 yrs	S,L
11	M	49	Cauc.	5 yrs	5 yrs	S
12	M	27	Cauc.	5 yrs 6 mths	5 yrs 6 mths	S
13	M	58	Cauc.	5 yrs	6 yrs	L
14	M	48	Cauc.	7 yrs	7 yrs	L
15	M	55	Cauc.	8 yrs	8 yrs	S,L
16	M	61	Cauc.	8 yrs	8 yrs	L
17	M	29	Cauc.	10 yrs	12 yrs	L
18	M	60	Cauc.	12 yrs 6 mths	12 yrs 6 mths	S

S = Solid formulations of paraquat

L = Liquid formulations of paraquat

TABLE 2.3 DETAILS OF KELANG (MALAYSIAN) WORKFORCE

Subject	Sex	Age (years)	Ethnic group	Total period of exposure to paraquat	Length of time from first exposure to paraquat	Formulations handled
1	M	39	Malay	6 mths	6 mths	L
2	M	30	Chinese	1 yr	1 yr	L
3	M	27	Malay	2 yrs	2 yrs	L
4	M	32	Malay	2 yrs	2 yrs	L
5	M	30	Indian	3 yrs	3 yrs	L
6	M	33	Indian	3 yrs	3 yrs	L
7	M	24	Indian	7 mths	3 yrs	L
8	M	37	Malay	3 yrs	3 yrs	L
9	M	34	Chinese	3 yrs	3 yrs	L
10	M	24	Malay	8 mths	3 yrs 6 mths	L
11	M	23	Malay	3 yrs 6 mths	3 yrs 6 mths	L
12	M	23	Malay	4 yrs	4 yrs	L
13	M	23	Malay	1 yr 3 mths	4 yrs	L
14	M	28	Indian	4 yrs	4 yrs	L
15	M	27	Malay	8 mths	5 yrs	L
16	M	32	Malay	6 mths	6 yrs	L
17	M	31	Malay	2 yrs	6 yrs	L
18	M	26	Malay	6 yrs 6 mths	6 yrs 6 mths	L

L = Liquid formulations of paraquat

TABLE 2.4 WORKER EXPOSURE PATTERNS TO PARAOQUAT

Length of time from first exposure to paraquat	YALING		KELANG		TOTAL	
	No. of workers	% of group	No. of workers	% of group	No. of workers	% of total
More than 10 years	2	11.1	-	-	2	5.5
8-10 years	2	11.1	-	-	2	5.5
5-7 years	4	22.2	4	22.2	8	22.2
Less than 5 years	10	55.5	14	77.7	24	66.7
Totals	18	100	18	100	36	100

including the other commonly used bipyridyl, diquat. Exposure to paraquat is most likely to occur in charging the system or at filling out, or when a blockage in the system is cleared. The solid formulations of paraquat contain 2.5 percent of paraquat ion (plus 2.5% diquat) and exposure was highest when freshly produced granules were removed from the drying trays. Considerable amounts of dust were produced in the drying process and in the early days of formulation the level of housekeeping was not always satisfactory. These problems have now been overcome by total enclosure of the formulation process and the use of extraction ventilation where the sachets are automatically filled and sealed.

(b) Survey

The medical records of both groups of workers were examined. These record all significant episodes of ill health, sickness absence and any accidents or injuries. A questionnaire was applied by the medical staff of the plant which included previous employment history, exposure to other pesticides, past medical history, concentrating particularly on any history of skin, respiratory tract or gastro-intestinal conditions, together with smoking habits and other addictions. The clinical examination was directed particularly towards any evidence of chronic skin conditions. It was not possible at the time this study was undertaken to perform tests of alveolar diffusion, although these were carried out in a subsequent study of spraymen.

RESULTS AND DISCUSSION

The incidence of clinical problems associated with exposure

to paraquat is set out in table 2.5. The occurrence of numerous episodes resultant upon direct contact with paraquat indicates a degree of significant exposure in both groups of workers.

There were a number of acute skin rashes, burns and eye injuries at the Kelang plant, and this may reflect the lower level of safety consciousness amongst the Malaysian workers. Skin contact with paraquat usually produced a delayed caustic effect consisting of erythema with occasional formation of bullae. In most cases healing was normal, although in one case with severe scrotal inflammation through careless spillage of paraquat concentrate healing took over two weeks. Eye splashes were followed by intense conjunctivitis with blepharospasm and lacrymation. In none of these cases, however, was there any evidence of permanent damage to skin, conjunctivae or cornea, nor was vision impaired in any case. The particular problem among the workers handling solid formulations was the occurrence of occasional epistaxes. In the majority of cases the phenomenon was encountered within the first week or so of working with the solid formulation and thereafter the incidence of epistaxes fell off rapidly. In no case was there frank bleeding and the invariable complaint was frequent spotting of the handkerchief with blood after blowing the nose.

The only two conditions found in these workers which could be called chronic effects of paraquat exposure were the occasional complaints of blepharitis and the phenomenon of delayed healing. Blepharitis was reported by only three of the thirty six

TABLE 2.5. INCIDENCE OF CLINICAL PROBLEMS ASSOCIATED WITH PARAOQUAT EXPOSURE

	YALDING GROUP		KELANG GROUP		TOTAL Number	% of total
	Number	% of group	Number	% of group		
(a) LIQUID FORMULATIONS ONLY						
Acute skin rashes	0	0	9	50	9	36
Nail damage	2	28.6	1	5.5	3	12
Epistaxis	1	14.3	2	11.1	3	12
Eye injuries	0	0	6	33.3	6	24
Blepharitis	0	0	1	5.5	1	4
Delayed healing	0	0	1	5.5	1	4
No complaints	4	57.1	3	16.6	7	28
(b) SOLID FORMULATIONS ONLY						
Nail damage	3	37.5	3	37.5	3	37.5
Epistaxis	7	87.5	7	87.5	7	87.5
Blepharitis	1	12.5	1	12.5	1	12.5
Delayed healing	1	12.5	1	12.5	1	12.5
No complaints	0	0	0	0	0	0
(c) BOTH LIQUID AND SOLID FORMULATIONS						
Nail damage	2	66.6	2	66.6	2	66.6
Epistaxis	2	66.6	2	66.6	2	66.6
Blepharitis	1	33.3	1	33.3	1	33.3
Delayed healing	2	66.6	2	66.6	2	66.6
No complaints	0	0	0	0	0	0

n = No. of workers

workers and in each case it was very mild. Symptoms subsided rapidly after removal from work. Delayed healing manifested itself as a failure of small lacerations and abrasions to heal spontaneously in the usual time. Small wounds tended to remain open for several days with the increased risk of infection. Only four of the workers complained of this problem, three of whom had handled the solid formulations. The problem resolved as soon as the worker was removed from exposure to paraquat and the condition appears to be a function of skin contamination and, as such, probably reflects lack of hygiene.

Examination of the skin of all workers provided no evidence of the development of chronic skin conditions following exposure to paraquat. Hyperkeratosis has been described following exposure⁵³, but none of these two groups of workers showed any evidence of this type of lesion, nor did they show any eczematous lesions. No allergic type rashes were found, nor was there any history among these workers of allergic manifestations to paraquat. Although this study did not isolate control groups of workers not exposed to paraquat, the medical records of all workers were available and apart from the usual distribution of various clinical conditions, which appeared common to all workers, especially upper respiratory tract infections at both plants and mild gastro-intestinal upsets at Kelang, there was no other clinical evidence of chronic ill health amongst these men following prolonged exposure to paraquat. Further, none of them attributed any illness, apart from the acute episodes, to their work.

2.4.2. LONG TERM PARAQUAT SPRAYING

In order to investigate the real degree of risk associated with the long term spraying of paraquat a group of workers on Malaysian plantations was studied. The sprayworkers in the study had used large quantities of paraquat for considerable periods of time and the study was designed to estimate the degree of genuine exposure under normal working conditions, and also to determine whether such long-term spraying has any measurable effects. To this end the spraymen were compared with two control groups. One was a group of general workers, some of whom occasionally may work in areas recently sprayed, and the other was a group of latex processing factory workers who had received no known exposure to paraquat in the course of their work. The clinical aspects of this study have been published⁶.

METHODS

(a) Population

The workers studied were drawn from six rubber and oil palm estates in Melaka and Negri Sembilan States of Peninsula Malaysia as a result of the ready co-operation of Dunlop Estates Sdn. Bhd. From the standpoint of any epidemiological studies, Malaysia has the advantage over many areas in enjoying tropical rainfall conditions which ensure weed growth throughout the year. Consequently, spraying programmes continue throughout the year so that spraying continues on a daily basis, rather than the intermittent seasonal type of spraying which is characteristic of temperate climates. Furthermore, the rubber and oil palm estates are virtually unique in that there is almost no insecticide spraying and it was thus possible to isolate a group of sprayworkers

who had sprayed only herbicides, of which the predominant chemical was paraquat. It is worth noting that paraquat is probably the major herbicide used throughout South East Asia, and particularly in Malaysia. As a result, the sprayworkers not only use considerably larger quantities of paraquat each year than those in temperate climates, but this is used on a continuous basis and the spraymen are also free from the problem of mixed exposure that is usually met in Europe and USA where spraymen will handle a large variety of different types of pesticide (herbicides, insecticides, fungicides, etc.) in the course of a year. No spraymen were included in this study who were from those estates where insecticides and other pesticides (such as fungicides) were used. This excluded estates which were being developed for cocoa bean production on which insecticides are used extensively.

Two control groups were chosen and consisted of general plantation workers and latex factory workers. The original intention had been to use two groups of estate workers as controls, one of rubber tappers and oil palm harvesters and the other of general manual workers. It was discovered, however, that some of the tappers and harvesters had been employed in spraying operations and had, therefore, to be excluded. Because of this and the small number of general workers available, it was decided to consider both tappers and harvesters together with the general manual workers as a single control group (called general workers). The study

was limited to male workers as there were very few female spray operators and their data contained too little information for formal statistical analysis.

The following criteria were used in selection. Spraymen were defined as those who had sprayed a minimum of 1,000 hrs. General workers were defined as those plantation workers who had no history of spraying and were employed in a variety of manual duties such as tilling, weeding, tapping and harvesting. Some members of this group had received minimal exposure to paraquat as a result of working in areas of the plantations in which spraying had recently been completed.

The factory workers were those employed on the estate 'factories' where the raw latex is given initial processing to prevent bacterial decomposition and render it fit for travel. Two highly irritant chemicals are used in this process; formic acid and ammonia. Ambient concentrations, however, rarely reach levels that produce irritation of mucous membranes. Occasional spillages occur, but these rarely produce problems as workers wear rubber aprons, gloves and boots. None of these workers had any known occupational exposure to paraquat. All three groups had similar social backgrounds and resided together in the same estate villages. The workers normally worked an eight hour day for six days per week, with two weeks leave each year and an allowance of two weeks sick leave. As a result of this selection, the three

groups finally consisted of 27 spraymen, 25 general workers and 23 factory workers. An analysis of the age and racial structure of the whole group is given in table 2.6.

(b) Exposure to Paraquat at Work

The spraying history of each sprayworker was obtained at a preliminary interview which also recorded the extent of any protective clothing worn during spraying operations, together with any episode of ill health attributable to occupation such as skin rashes. These were later cross-checked with individual medical records. The total amount of paraquat sprayed per year on each estate was obtained from company records, and by combining these figures with the spraying record of each man it was possible to produce an estimate of the amount of paraquat each had used. Paraquat is normally sprayed on the estates at a rate of approximately 0.1% paraquat ion, frequently in a tank mix with diuron and mono-sodium methane arsenate and also one of the phenoxy alkylates to ensure a wide spectrum of weed control. Workers generally did not wear any protective clothing during spraying operations. The normal dress consisted of a shirt, singlet, underpants and cotton trousers. These were usually tucked into the socks when working. Footwear varied from rubber boots to canvas or leather shoes or even open sandals. Table 2.7 shows the amount of protection used. Spraymen regularly showered after work and changed their clothes, but rarely bothered to wash off minor splashes and only infrequently washed before eating when in the field. Work clothing was only infrequently laundered.

TABLE 2.6 AGE AND RACIAL STRUCTURE OF WORKING GROUPS

Age (yrs)	SPRAYMEN			GENERAL WORKERS			FACTORY WORKERS			TOTALS						
	Malay	Indian	Chinese	Total	Malay	Indian	Chinese	Total	Malay	Indian	Chinese	Total				
Less than 25	5	1	1	7	2	2	1	5	11	1	0	12	18	4	2	24
25-34	4	5	0	9	3	4	3	10	4	1	0	5	11	10	3	24
35-44	2	3	0	5	2	1	3	6	2	1	0	3	6	5	3	14
45 and over	3	1	2	6	1	2	0	3	0	1	2	3	4	4	4	12
TOTALS	14	10	3	27	8	9	7	24	17	4	2	23	39	23	12	74

TABLE 2.7 DEGREE OF PERSONAL PROTECTION USED BY SPRAYMEN

TYPE OF PROTECTION	No.	%
Overalls or plastic apron with rubber boots	1	3.7
Rubber gloves with rubber boots	2	7.4
Rubber boots only	8	29.6
Rubber gloves only	1	3.7
No protection used	15	55.6
	27	100

Conditions varied slightly from estate to estate. However, in all cases the terrain consisted of low hill country with gentle undulations. Rubber and palm trees were laid out in uniform contour planting with secondary growth developing between. This consisted of a mixture of grasses, ferns and perennial broadleaf weeds, which at times could be as high as 120 cm, although usually about 45 to 90 cm in height. This meant that as the spraymen walked forward into the sprayed area there was potential dermal contamination from spray 'run-off' to waist height. Measurements were made of the extent of potential dermal and inhalational exposure in a series of environmental monitoring procedures (see below). Either Saval or Birchmeier knapsack sprayers were used, with standard flowjet, solid cone or 'polijet' nozzles.

A further source of potential exposure came at the first stage of mixing. Mixing procedures varied from estate to estate. In some, all mixing was done centrally at the chemical store in large tractor drawn tankers and the paraquat concentrate was handled under very well controlled conditions. The dilute spray solution was transported around the estate as and when required. On other estates, however, the concentrate was diluted on the field using water dispensed from a transportable tank (fig 2.5). Inevitably, even though it was normal practice for only one member of the spraying team to be responsible for diluting the concentrate, the potential for spillages and other accidents was much greater in the field

FIG. 2.5: FIELD MIXING OF AGRICULTURAL CONCENTRATE



Photo: the author

than under the more easily controlled conditions at a central chemical store.

(c) Clinical Examination*

All the workers were given a full clinical examination with particular attention being paid to respiratory system and skin.

(d) Clinical Measurements

The workers were all examined at a central site, one of the Estate hospitals and at approximately the same time, between 10.00 and 12.00 hours on several succeeding days. Blood was taken for haematological examination, liver and renal function tests, using standard venepuncture technique from the ante-cubital vein. Plain tubes were used for blood for liver function, heparinised tubes for renal function tests and Sodium EDTA was the anti-coagulant for the haematological specimens. All containers were stored in ice and transported to the laboratories in Kuala Lumpur (90 miles away) within three hours of specimens being taken. Measurements were completed by 16.00 hours the same day. The following indices of normal function were used:

(i) Respiratory function Ventilatory function was measured by FVC, FEV₁ and FEV% using the standard 'Vitalograph' Spirometer and digital display meter. Three readings were taken on each subject and the highest value achieved was used. Transfer factor (DCO), as an

* Clinical examinations were undertaken by Dr. N.N. Sabapathy (Chief Medical Officer, Dunlop Estates, Melaka).

estimate of alveolar diffusion, was measured by a single breath method, using the Hewlett Packard 47404A Single Breath Carbon Monoxide Diffusion System. The higher of two values was used.

- (ii) Liver function* This was determined by estimations of the activity of the following enzymes, using the Hycel Super 17 Auto analyser : Serum alanine aminotransferase (ALT) using L-alanine and α -ketoglutarate as the substrate and acidic 2, 4, dinitrophenyl hydrazine as the colour reagent. Serum aspartate aminotransferase (AST), using L-aspartate and α - ketoglutarate as the substrate and Fast Violet B as the colour reagent and alkaline phosphatase (ALKP) using magnesium thymolphthalein monophosphate as the substrate and the addition of alkali to induce the colour reaction.
- (iii) Renal function* An estimate of renal function was made by the determination of blood urea nitrogen using the diacetyl/thiosemicarbazide colorimetric method with the Hycel Super 17 auto analyser and the determination of serum creatinine using a manual endpoint colorimetric method with picric acid. Urine albumen tests were also performed simply at the time of the initial clinical examination by the semi-quantitative Ames strip method.
- (iv). Haematology* Haemoglobin estimations were made by the colorimetric cyanmethaemoglobin method using the Hycel Model 700 automated counter which also gave red and white

* Laboratory investigations were undertaken by Dr. H. Kaur (Computer Med Lab, Kuala Lumpur)

cell counts, PCV, MCHC, MCH and MCV. The differential white cell count was performed manually after staining the blood slide with Leishman's stain.

(e) Environmental Measurements*

In order to obtain a measurement of the dermal and respiratory exposure of the spray operators, four groups of male spray operators were randomly selected and measurements were undertaken during a typical working day.

(i) Dermal Exposure This was measured using a modification of the standard WHO protocol⁵⁴. Dermal exposure pads, consisting of polythene backed Whatman grade 542 filter papers with a surface area of 80 cm², were applied to the skin (if directly exposed) or clothing at the following sites:

Left arm:	mid-forearm
	mid-upper arm
Left leg:	mid-lower leg (or below knee if boots worn)
	mid-thigh
Trunk:	over sternum
	'V' of neck
	lower back beneath knapsack container
Head:	forehead

* The actual environmental sampling was carried out by G. Chester and paraquat analysis of samples was undertaken by B.H. Woollen, both of ICI Ltd., Central Toxicology Laboratory, Alderley Park, Cheshire.

The pads were removed at the end of the spraying operation and stored individually in polythene containers for transport to UK for paraquat estimations.

(ii) Respiratory exposure was measured using standard Rotheroe-Mitchell L25F personal air samplers, operating at a flow rate of 2 litres min⁻¹. The sampling heads were in the sprayman's breathing zone. Paraquat aerosol was collected onto Whatman Number 1 or 542 filter paper in the sampling head. These filters have collection efficiencies of 100% for particle sizes down to 2 micron diameter. In addition urine samples were collected from each sprayman each day immediately after spraying. Samples were stored on ice in individual polythene containers with azide preservative pending analysis for paraquat.

(iii) Paraquat analysis The radio-immunoassay method developed by Levitt⁵⁵ was used for the estimation of paraquat in the urine samples and on the filters from the personal air samplers. The filter papers used for the estimate of dermal contamination were analysed using a modification of the method of Calderbank and Yuen⁵⁶. In this method paraquat is extracted from the sample by shaking in saturated ammonium chloride and the extract mixed with sodium dithionite. The amount of paraquat present is calculated from the absorbance of this solution at 600 nm.

(iv) Method of calculation The dermal exposure data were adjusted to uniform time and extrapolated from mg/paraquat ion per 25 cm² filter paper to mg/paraquat

ion per body part per hour to calculate the dermal exposure of individual body parts. The body part surface areas given in the WHO Standard Protocol were used for this extrapolation. As these areas have been derived for a 70 kg Caucasian they have been reduced proportionally to take into consideration the lower mean body weight, height and total surface area of South East Asians as indicated from the heights recorded in Appendix 2.2. In order to calculate the latter, a height-area-weight nomogram was used ⁵⁷. The mean bodyweights and heights employed (males only) were:

weight: male - 60 kg;

height: male - 162.5 cm;

On this basis, the following body surface area was derived:

for male - 1.65 m^2 ;

The respiratory exposure data were adjusted to mg paraquat ion per metre ³ air using the sampling rate and times, and hence the total volume of air sampled.

RESULTS

(a) Amount of paraquat used

Each estate taking part in this study used between 950 and 2050 litres of 'Gramoxone' (the 20% agricultural concentrate) per annum depending on area and size of the spray team. This represents an average annual quantity of approximately 336 litres of 'Gramoxone' sprayed by each spraymen, equivalent of 67.2 kg paraquat ion. The mean length of time the spraymen in this study had worked was 5.3 years, representing a mean of 8,696 actual spraying hours per man. Some workers, however, had been involved in regular spraying operations with paraquat since 1966 (i.e. for 12 or 13 years at the time of the study).

(b) Adverse responses to paraquat

There were 11 spraymen out of 27 who complained of one or more incidents of skin irritation/rashes associated with spraying. These were commonest on hand, legs or groin. In the case of groin/buttock rashes these were commonly associated with a leaking knapsack sprayer which had allowed material to run down the back and between the legs and buttocks. Medical records indicated that all cases cleared rapidly, usually in a few days, in response to local treatment (usually a steroid cream). Although 12 of the spraymen admitted to having been involved in spillages or splashes of material, only one case of eye injury had been reported and this had responded with no sequelae.

(c) Clinical measurements*

To test the effect of occupational exposure to paraquat, comparisons were made between sprayers, general workers and factory workers for each of the fifteen clinical measurements. The significance of occupation was tested with allowance made for difference in the distributions of race, age, height and smoking history between the three groups. This was achieved by fitting multiple regression equations with race, age, height and smoking history as the independent variables and then by refitting the equations with occupation added as a further independent variable. The decrease in the residual sum of squares thus achieved was tested for significance using an F-test. Details of the independent variables used and the regression equations fitted involving all variables are given

* The statistical calculations were undertaken by P. Anne Whitehead (Statistician, ICI Ltd, Plant Protection Division, Bracknell, Berks)

in Appendix 2.1, and the full results used in the study are set out as Appendices 2.2, 2.3 and 2.4.

Estimates of the effect of occupation on the clinical measurements can be obtained from these regression equations. For example with FVC, then if a sprayer, general worker and factory worker had the same race, age, height and smoking history, then the sprayer would be expected to have an FVC value 0.139 higher than the factory worker, 0.048 lower than the general worker, and the general worker 0.187 higher than the factory worker. Tables 2.8, 2.9 and 2.10 show the estimated values for each of the occupations for Malay, Indian and Chinese males aged 30 years, height 162.5 cm and non-smokers. The tables show the significance of the differences between the occupations (the probability level for the F-test). The standard error (person) is a measure of the deviation of an actual observation from the regression equation. The tables also show the probability level for the test of significance of the occupation. The Lowest Significant Difference (LSD) $P = 5\%$ is given when differences between occupations are significant at the 5% probability level. If the estimates for two groups of workers differ by more than the LSD then this suggests a significant occupational effect.

No significant differences could be demonstrated for the respiratory or haematological indices. However, significant differences were found for both liver and renal measurements and in each case it was the factory workers who differed from both spraymen and general workers. Both levels of serum

TABLE 2.8 ESTIMATED CLINICAL VALUES (MALAY)

These values have been estimated using the regression equations in Appendix 2.1 for a Malay non-smoker, male, aged 30, height 162.5 cm

	FVC (litres)	TVC (litres)	FEV ₁ %	DCO (mmol/ min/kpa)	Hb (g/dl)	PCV	NEC (millions/ ul)	NCO ₃ (um)	MCH (pg)	log ₁₀ MBC (ul/g)
STRAYEN	3.28	2.94	90.0	11.6	14.3	41.6	5.31	77.9	27.0	3.916
GENERAL WORKERS	3.33	2.94	88.3	12.4	15.0	43.3	5.54	77.9	27.0	3.959
FACTORY WORKERS	3.14	2.80	89.0	12.2	14.6	43.5	5.57	77.5	26.3	3.935
STANDARD ERROR (PERSON)	0.49	0.44	7.5	1.9	1.3	3.5	0.50	5.2	2.2	0.009
DIFFERENCES BETWEEN OCCUPATIONS	P= 48%	P= 51%	P= 73%	P= 30%	P= 21%	P= 13%	P= 16%	P= 96%	P= 52%	P= 5.3%
LSD P = 5%	S v GW	S v FW	GW v FW							

	log ₁₀ AST (IU/l)	log ₁₀ ALT (IU/l)	ALT (IU/l)	log ₁₀ ALKP (IU/l)	ALKP (IU/l)	log ₁₀ CREAT (mg/dl)	CREAT (mg/dl)	log ₁₀ BUN (mg/dl)	BUN (mg/dl)	
SPRAYMEN	1.315	20.7	1.597	39.5	1.510	32.4	-0.013	0.97	1.031	10.7
GENERAL WORKERS	1.286	19.3	1.561	36.4	1.463	29.0	-0.075	0.84	1.023	10.5
FACTORY WORKERS	1.345	22.1	1.167	14.7	1.599	39.7	0.025	1.06	1.107	12.8
STANDARD ERROR (PERSON)	0.153	0.227	0.115							0.103
DIFFERENCES BETWEEN OCCUPATIONS	P= 51%	P<0.01%	P= 0.3%					P= 3.4%		P= 2.0%
LSD P = 5%	S v GW	0.134	0.068					0.067		0.060
	S v FW	0.134	0.068					0.067		0.061
	GW v FW	0.144	0.073					0.072		0.065

TABLE 2.9 ESTIMATED CLINICAL VALUES (TRIANS)

These values have been estimated using the regression equations in Appendix 2.1 for an Indian, non-smoker, aged 30, height 162.5 cm.

	\log_{10} AST	AST (IU/l)	\log_{10} ALT	ALT (IU/l)	\log_{10} ALAT ^a ALAT ^b	AIKPF (TU/l)	\log_{10} CREAT	Creat (mg/dl)	\log_{10} BUW	BUW (mg/dl)
SPLATTER	1.362	23.0	1.771	59.0	1.497	30.7	0.055	1.14	1.005	10.1
GENERAL WORKERS	1.353	21.5	1.734	54.2	1.439	27.5	-0.006	0.99	0.997	9.0
FACTORY WORKERS	1.392	24.7	1.341	21.9	1.576	37.7	0.094	1.24	1.031	12.1
STANDARD ERROR (PERSON)	0.153		0.227		0.115		0.113		0.103	
DIFFERENCES BETWEEN OCCUPATION	P= 51%		P<0.01%		P= 0.3%		P= 3.4%		P= 2.8%	
LSD P = 5%	S v GM		0.134		0.068		0.067		0.060	
	S v FM		0.134		0.068		0.067		0.061	
	GM v FM		0.144		0.073		0.072		0.065	

TABLE 2.10 ESTIMATED CLINICAL VALUES (CHINESE)

These values have been estimated using the regression equations in Appendix 2.1 for a Chinese, non-smoker, aged 30, height 162.5 cm.

	FVC (litres)	FEV ₁ (litres)	FEV ₁ %	DCO (nmol/ min/kpa)	Hb (g/dl)	PCV (millions/ ul)	RCG (pg)	MCV (nm ³)	log MBC	VTC (mc/uL)
SPRAYEN										
GENERAL WORKERS	3.47	3.14	91.9	11.6	13.7	40.4	5.35	75.4	25.9	3.910
FACTORY WORKERS	3.51	3.14	90.2	12.5	14.4	42.1	5.59	75.4	25.9	3.851
	3.53	3.00	90.9	12.3	14.0	42.3	5.62	75.0	25.2	3.928
STANDARD ERROR (PERSON)										
DIFFERENCES BETWEEN OCCUPATIONS	0.49	0.44	7.5	1.9	1.3	3.5	0.50	5.2	2.2	0.099
LSD P = 5% S v GM	P = 48%	P = 51%	P = 75%	P = 30%	P = 21%	P = 13%	P = 16%	P = 96%	P = 52%	P = 5.3%
S v FW										
GM v FW										

	log 10 SGOT (TU/l)	log SGPT ¹⁰ (TU/l)	SGPT (TU/l)	log 10 ALAT ¹⁰	AIKP (TU/l)	log CREAT ¹⁰ (mg/dl)	CREATAT (mg/dl)	log 10 BUN ¹⁰	log BUN	BUN (mg/dl)
SPRAYEN										
GENERAL WORKERS	1.276	18.9	1.492	31.0	1.454	28.4	-0.008	0.70	1.019	10.4
FACTORY WORKERS	1.247	17.7	1.456	28.6	1.406	25.5	-0.069	0.85	1.011	10.3
	1.306	20.2	1.062	11.5	1.543	34.9	0.030	1.07	1.095	12.4
STANDARD ERROR (PERSON)										
DIFFERENCES BETWEEN OCCUPATIONS	0.153	0.227	0.115	0.113						
LSD P = 5% S v GM	P = 51%	P < 0.01%	P = 0.3%	P = 3.4%						
S v FW		0.134	0.068	0.067						
GM v FW		0.134	0.068	0.067						
		0.144	0.073	0.072						

creatinine and blood urea nitrogen were significantly higher in this group, as was also the level of serum ALK activity.

The level of serum ALT activity, however, was significantly lower in factory workers than the other two groups. All group means, however, fell within the levels quoted as normal by the laboratory undertaking the estimations.

Further investigations into the effect of spraying on DCO and Hb estimations were carried out by correlating the residuals of both DCO and Hb from the regression equations in Appendix 2.1 with log total number of spraying hours. In neither case was the correlation statistically significant. All values relating to erythrocytes were lower than corresponding Caucasian values.

Age and height were significant variables with FEV_1 , and FVC measurements and age was a significant variable in respect of $\text{FEV}_1\%$ and DCO values. A racial trend appeared to exist with DCO values, Indians showing slightly lower values. The mean values and range, however, were comparable with figures obtained from 'normal' Caucasians.

Smoking did not appear as a significant variable in the respiratory measurements, which almost certainly is to be related to the fact that of the 74 subjects only 9 smoked more than 15 per day, and only 2 more than 25 per day. 30 were non-smokers and 22 smoked between 1-10 cigarettes per day.

(d) Environmental measurements

- (i) Dermal exposure The calculated dermal exposures for the spray operators are shown in table 2.11. Individual body

parts have been separated into two categories according to whether they were clothed or not. Two estimates of total exposure are given. The first is a summation of individual exposures of unclothed areas (i.e. those body parts such as hands and head not normally covered), which is the recommended procedure given in the WHO Standard Protocol. The second is a summation of unclothed and clothed body areas and is recorded as a potential total exposure. Similarly, two estimates of dermal dose are given. The distinction has been drawn because the former interpretation assumes that the clothing worn by a spray worker affords him a measure of protection from dermal contamination with sprayed pesticide, whereas the latter allows estimation of the total potential exposure. The second figure is important in view of the ready permeability of cotton materials worn in South East Asia to water soluble pesticides.

There were large differences between unclothed total and overall total exposures for each spray operator (table 2.11). The mean unclothed exposure was 2.48 mg paraquat ion per hour of spraying with individual variation from zero to 12.3 mg paraquat ion per hour of spraying. The mean value of 2.48 mg/hour is equivalent to a dermal dose of 0.04 mg/kg/hour. The highest individual direct dermal exposure of 12.3 mg/hour is equivalent to 0.2 mg/kg/hour. The mean overall total exposure was 72.04 mg paraquat ion per hour, with individual variation from 12.1 mg/hour to

TABLE 2.11 DERMAL EXPOSURE OF SPRAY OPERATORS

Batch No.	Worker	Exposed Body Parts Head Neck Shoulders Hands Forearms	Dermal Exposure (mg Paracetamol/Hour)						Dermal Dose (mg/kg/hr)		
			Forearms	Upper Arms	Sternum	Buttocks	Thighs	Lower Legs	Direct Exposure of Exposed Body Parts (mg/hr)	Total Exposure (Potential) mg/hr)	Cumulative Exposed
1	1	ND	0.53	0.79	ND	ND	ND	ND	1.32	87.8	0.02
	2	0.76	ND	0.1	ND	ND	ND	ND	5 ⁻³	8x10 ⁻³	1.5
	2	0.70	0.04	0.21	0.22	0.35 ^a	0.45 ^a	0.5	0.46	5 ⁻¹	0.0
	4	ND	0.05	ND	2.53	ND	ND	2.2	1.26	114.3	0.02
									2.58	126.9	0.04
2	1	ND	0.17	ND	1.57	2.35	1.00	ND	1.09	17.31	No Rd
	2	ND	ND	ND	0.21	0.31	ND	ND	0.42	16.16	145.29
	3	ND	0.04	ND	3.24	1.84	1.23	ND	0.13	49.28	17.02
	4	ND	ND	ND	ND	ND	4.65	ND	6.20	3.28	76.6
									7.90	39.75	0.05
7	1	ND	0.03	ND	2.24	3.35	0.21	ND	0.24	14.04	21.28
	2	ND	ND	ND	ND	ND	ND	ND	No Rd	3 ⁻⁵	2.27
	3	ND	ND	ND	0.22	0.33	ND	ND	6.04	8.54	ND
	4	ND	0.04	ND	0.37	0.56	0.29	ND	0.55	11.79	29.32
									51.41	42.72	0.55
4	1	ND	0.02	ND	1.0	1.50	0.21	ND	0.71	23.40	24.12
	2	0.63	0.56	0.17	6.4	6.56	5.9	ND	ND	25.41	21.0
	3	1.77	0.75	0.47	4.74	7.09	5.04	ND	ND	17.05	26.7
									7.73	51.0	0.04
										64.6	0.2
										63.6	0.1
Mean	SP								2.48	72.04	0.04
									3.34	40.0	0.05
											1.21
											0.59

ND - None Detected

Lower limit of detection is 10 ng/filter

162.4 mg/hour. The mean value is equivalent to a dermal dose of 1.21 mg/kg/hour. The highest individual "total" exposure of 162.4 mg/hour is equivalent to 2.7 mg/kg/hour.

(ii) Respiratory exposure The mean paraquat concentration in the air of the sprayman's breathing zone was calculated to be 1.03 ug paraquat ion / m³ (table 2.12). This figure represents the total air concentration of paraquat and not that occurring as respirable sized droplets which would be a much lower concentration, although, in view of climatic conditions it is likely that the figure would be higher than Hogarty's ³⁵ estimate of 50% of droplets in the breathing zone as the maximum.

(iii) Urine analysis Paraquat residues were detected in the urine of six out of fifteen spray operators (table 2.13). The levels are remarkably close to those reported by Swan ten years earlier ⁵.

DISCUSSION

The results of the environmental measurements indicate that the spray worker is exposed to comparatively large amounts of paraquat in the course of his work. Actual dermal exposure may be considered to lie somewhere between the two calculated extremes of 2.1 mg and 63.1 mg paraquat ion per hour. Such figures are significantly higher than those obtained by Staiff ³⁴ in his study of sprayer operators using tractor mounted equipment. It is apparent from the results recorded in table 2.11 that the greatest potential contamination was on the legs. Hands also represented a significant source of possible absorption and in further studies of this worker population Chester and Woollen ⁵⁸

TABLE 2.12 RESPIRATORY EXPOSURE OF SPRAY OPERATORS

Dunlop Estate	Worker	Total Paraquat Ion per Sampler Filter (g)	Sampling Duration (min)	Total Volume of Air Sampled (l)	Air Concentration (g/m ³)
1	3	0.67	60	120	0.67
	4	0.68	135	240	2.8
2	3	0.41	200	400	1.0
	4	0.16	200	400	0.4
3	1	0.28	160	320	0.88
	2	0.27	160	320	0.84
4	1	0.28	225	450	0.62
	Mean				1.03
	SD				0.8

TABLE 2.13 PARAQUAT RESIDUES IN URINE

Workers	Paraquat Residues mg/litre			
	Dunlop Estate			
	1	2	3	4
Spray Operators				
1	0.05	0.08	0.05	0.05
2	0.05	0.19	0.05	0.05
3	0.05	0.05	0.35	0.09
4	0.05	0.05	0.05	-

Mean value (all spraymen) 0.05 mg/litre (SD 0.1)

Mean value of residues detected 0.14 mg/litre (SD 0.12)

Lower limit of detection is 0.05 g/ml

have shown that hand contamination may exceed that of the legs due to careless work practices. Spray nozzles are frequently handled in order to align them correctly or unblock them, and operators were even observed to wash their hands in the diluted formulation in the spray tank after oiling the knapsack sprayer mechanism.

The fact that such exposure was associated with dermal absorption was reflected in the urinary levels of paraquat. Although these data must be treated with caution as the results are little more than 'spot checks', they do bear comparison with the figures obtained by Swan⁵. His measurements were made on 24 hour specimens, but none the less the figures from both studies are in the same order. It is thus likely that some of the workers studied have been excreting paraquat in their urine for up to 12 years continuously in view of their long spraying history since 1966.

The minor importance of inhalation as a route for absorption was confirmed in this study. The total amount of paraquat in the breathing area was very small, even less than in Hogarty's Irish study³⁵. Furthermore, studies on the droplet size distribution have demonstrated that the percentage of droplets within the respirable range is normally less than half the total^{35, 56}. Even allowing for a higher percentage as a result of climatic conditions, the total 'inhalable' paraquat is an insignificant amount.

The extent of such a degree of potential exposure over many

years has led to concern being expressed about the possibility of systemic poisoning arising as a result of normal spraying operations. This study failed to show any clinical or biochemical evidence of organ malfunction, although claims have been made that the lung in particular may be affected by such operations^{9, 10}. The recent study by Levin and his co-workers⁷, to which reference was made at an earlier stage of this section, reported reduction in pulmonary function, particularly in the measurement of alveolar diffusion, as a result of spraying with paraquat. This present study of workers exposed daily for long periods, using large quantities of paraquat, and with evidence of paraquat absorption, failed to show any differences in lung function between sprayworkers and the two groups of controls. The range of values for ventilatory function did not differ in the three groups and the mean values were not significantly different. The values were also in close agreement with the 'normal' values obtained in other studies of Asian subjects⁶⁰⁻⁶², suggesting that the groups under study represented a 'normal' population. In none of the three groups of workers did occupation have any significant effect on ventilatory function, although, in agreement with all previously published work, FEV₁ and FVC values were related to both age and height. As expected, the values were consistently lower than those for Caucasians of equivalent age and height⁶³.

The assessment of alveolar diffusing capacity by the use of single breath Carbon Monoxide diffusion measurements (DCO) also showed no differences between the three working groups. This study, it is believed, is the first time that alveolar

diffusion has been measured in such an Asian population and no comparisons could be made with previously obtained normal values. However, the range of values is very close to those reported from studies of Caucasian subjects⁶⁴⁻⁶⁶.

Concern has also been expressed that exposure to paraquat may induce blood changes, in that there is a report of isolated instances of blood dyscrasias in cases of clinical paraquat poisoning⁶⁷. However, there has never been any evidence that exposure to paraquat under normal working conditions has had any effects on haematological parameters. In the present study there were no significant differences in the three working groups. Parameters associated with the red cell series were slightly lower than would have been expected in a comparable Caucasian group, but this is a general finding and reflects dietary habits and the effects of helminth infection (Kaur, 1979, unpublished observations), which were indicated by consistently high eosinophil counts in a large proportion of the population studied.

The effects of paraquat on both liver and renal function have been observed in severe poisoning following ingestion from the very first cases reported⁶⁸. Raised BUN and raised levels of serum ALKP and AST are regular features even in non-fatal poisoning cases. No such abnormalities were found in the group of sprayworkers. However, the factory workers did show some variation of both renal and liver function tests. These did not fall outside the range of normal values for the laboratory.

The few instances of local dermal lesions from poor spraying

techniques and accidents is indicative both of the high levels of training and supervision on the Dunlop Estates. No cases of nose bleeding were recorded and only one case of eye injury which recovered with no sequelae. The evidence of this study would indicate that paraquat spraying does not give rise to any serious health problems under conditions of proper usage, even with exposure levels considerably higher than those likely to pertain to temperate climates.

2.4.3. COMPARATIVE RISKS FROM HIGH AND LOW VOLUME SPRAYING TECHNIQUES

The studies described, taken in conjunction with the other published data, indicated that at normal spraying strengths (below 0.5% paraquat ion) there was unlikely to be any significant degree of risk for the spray operator, provided that proper agricultural practice was followed. Such studies, however, do not provide any data for assessing the risk associated with the use of higher ionic strength spray solutions. The introduction of spinning disc applicators such as the 'Herbi' (Micron Ltd) which utilise low volume/high concentration spray solutions has raised interest in their applicability over a wide range of herbicides. Such applicators have advantages over conventional spraying methods, especially in developing countries. They are frequently more efficient and because they use a lower volume of spray material to cover equivalent areas, the amount of water requiring to be transported and the amount of mixing that is necessary are greatly reduced when compared with conventional spraying methods. Consequently, there has been widespread (but unauthorised) use of paraquat with such equipment.

In view of the fact that the few fatalities which have occurred through the percutaneous absorption of paraquat have all been related to the use of high strength solutions, together with the fact that stronger spray strengths are likely to increase the risk of dermal irritation, it was considered necessary to investigate the degree of risk which low volume application presents to the spray operator. Accordingly, a risk assessment was linked with an efficacy trial in Thailand. The purpose was to compare the degree of dermal contamination produced by normal high volume knapsack spraying with that produced by low volume spraying techniques. At the same time urinary excretion of paraquat by the sprayworkers could be monitored and any clinical effects noted and comparisons made between the two groups of spraymen.

METHODS

Initial work in the UK, measuring the amount of leg and foot contamination from the 'Herbi' applicator, had suggested that it would be no more than from conventional equipment. Accordingly, the trial was mounted in Thailand using the following methods:

(a) Spraying equipment

Three different types of sprayers were used during the trial:

- (i) The Micron 'Herbi' standard model fitted with the yellow feed nozzle and with a guard for the spinning disc. No carrying straps were used initially but in due course the spraymen used strings, wires etc. to facilitate spraying.
- (ii) A standard Micron 'Herbi' combined with the 20 litre Allman back pack container instead of the 2.5 litre standard bottle reservoir.

- (iii) A Birchmeier Flox 10 knapsack sprayer fitted with the blue polijet nozzle.

In an experiment after the main trial period 3 standard 'Herbi' were compared with 3 modified machines with a 25 cm longer extension tube and fitted carrying strap.

(b) Herbicide

Commercial 'Gramoxone' (20% w/v paraquat ion) was used throughout the trial. For low volume spraying the daily requirement was prepared the previous evening in two 200 litre drums fitted with a tap. For knapsack spraying 'Gramoxone' was added to the water in the knapsack, which is the usual practice in Southern Thailand. The risks of accidental spillage are clearly much higher in this situation than in Malaysia, as described above. The application rates were:

- (i) Low volume: 20 litre/ha using 2% solution of paraquat ion (i.e. 2 litres 'Gramoxone'/ha)
- (ii) Knapsack: 250 litre/ha using 0.15% solution of paraquat ion (i.e. 1.87 litre 'Gramoxone'/ha)

(c) Spraymen

There were 14 spraymen at the beginning of the trial; 12 spraying low volume with the 'Herbi' and 2 spraying with the knapsack sprayers. However, one man left because of a death in his family and a second one was dismissed because of absenteeism, leaving 12 spraymen only, one of whom used a knapsack sprayer. All men wore a shirt and long trousers. There were 7 who were bare foot except for cheap rubber slippers which gave no protection to the dorsum of the foot. The remaining 5 wore plimsolls.

(d) Clinical*

Each man was given a chest X-ray and a thorough clinical examination before spraying began. Further clinical examinations at the end of each week of spraying and a final examination a week after spraying had been completed were undertaken. A further chest X-ray was also taken one week after spraying had finished. Urine samples were collected into sterile containers containing thymol preservative, for paraquat analysis, at the same time as the medical examinations and sent to Central Toxicology Laboratory in UK for the analysis. Equipment was not available to undertake biochemical, haematological or pulmonary function measurements and such measurements, although desirable, had to be omitted.

(e) Dermal Contamination

Absorbent cellulose pads (3M micro dressings) were fitted with staples on to an impermeable polythene base and then attached to the spraymen's outer clothing according to World Health Organisation protocols⁵⁴. They were applied as follows:

Arm: upper surface of left forearm, midway between elbow and wrist

Thigh: front of left mid thigh.

Leg: front of left leg, above the ankle

Foot: dorsum of left foot, below trouser leg.

Pads were removed at the end of the first period of spraying (at lunchtime after 4 hours' spraying). They were placed in

* Dr. S. Prasan of Pattaya, South Thailand, was responsible for the clinical examinations and X-rays.

labelled plastic bags and sent to the Environmental Sciences Section of Jealott's Hill Research Station in UK for analysis. A total of 6 measurements were made in association with the standard 'Herbi', 4 with the modified 'Herbi' and 4 with the knapsack sprayer.

(f) Spraying

The spraying programme was carried out in fields under cultivation with cassava (grown principally as an animal foodstuff and for the starch content: it is not used as a human nutrient in Thailand). At the time of spraying the cassava was about 100 cm high with undergrowth between the rows varying between 30 and 50 cm high. The terrain was hilly and spraying was carried out with the spraymen walking forward into the sprayed foliage. On the first spraying day the 'Herbi' was briefly explained to the team and demonstrated how it should be carried, but from then on the spraymen were free to hold it in their most convenient position. Spraying was done in a team accompanied by one supervisor. Hence every member of the group sprayed the same amount. The bottles were always filled by the supervisors. There was sufficient water available for the spraymen to wash their hands or other contaminated parts but it was the supervisors' policy not to urge them to do so (except in serious cases of contamination). Spraying began between 08.00 to 08.30 hours and went on until 17.00 hours with a 1 hour lunch break. Occasionally a group had to move to a new field and several times rain interrupted spraying, hence the shorter than

expected actual periods of spraying. However, each man worked for two periods of 5 days in the two week spraying programme.

RESULTS

The degree of dermal contamination by paraquat is shown in table 2.14. The amount of paraquat is expressed per 25 cm² of exposed surface as in World Health Organisation protocols. It was not considered necessary to extrapolate these figures to a time weighed exposure figure as the study was concerned only to compare two systems of spraying and not obtain absolute figures. The differences between the means of leg and foot contamination produced by the 'Herbi' applicator and by knapsack spraying were statistically significant using the Student 't' test (standard 'Herbi' versus knapsack: leg: - t = 3.17, df = 8, P < 0.01; foot: - t = 3.09, df = 8, P < 0.01; modified 'Herbi' versus knapsack: leg: - t = 2.00, df = 6, P < 0.05; foot: - t = 2.98, df = 6, P < 0.125).

The mean values of urinary excretion of paraquat are shown in table 2.15. There is a highly significant difference between the mean value of those using the 'Herbi' applicator without foot protection and those wearing shoes at the end of 14 days spraying, but not apparent at the end of the first week (t = 5.11, df = 9, P < 0.001).

All 14 spraymen who began the trial were clinically fit and chest X-rays showed no abnormalities. Two spraymen dropped out during the trial and therefore did not have final clinical

TABLE 2.14 SKIN CONTAMINATION: Mean values mg paraquat ion/25 cm²

	Number of Observations	Arm		Thigh		Leg		Foot	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Standard 'Herbi' applicator	6	0.19	0.38	1.31	0.86	5.29	1.81	10.66	3.26
Modified (long arm) 'Herbi' applicator	4	0.16	0.12	1.05	1.08	5.13	3.15	18.37	9.11
Knapsack sprayer	4	0.22	0.23	0.38	0.16	1.76	1.17	3.37	4.25

TABLE 2.15 URINARY EXCRETION OF PARAQUAT: Mean values mg paraquat ion/litre

	PRE-SPRAYING			SPRAYING			POST-SPRAYING		
	Day 0	Day 7	Day 14	Day 14	Mean	SD	Mean	SD	Mean
No. of Subjects									
Standard 'Herbi' applicator (wearing shoes)	5	ND	0.13	0.10	0.11	0.07	0.05	0.03	
Standard 'Herbi' applicator (with open sandals)	7	ND	0.20	0.14	1.05	0.40	0.08	0.10	
Modified 'Herbi' applicator (with open sandals)	1	ND	0.14	-	0.73	-	0.06	-	
Knapsack sprayer (with open sandals)	1	ND	0.96	-	0.21	-	0.02	-	

ND = None detected

examinations. Only one sprayworker remained trouble free at the end of the 14 days' spraying, although one of the incidents reported (acute diarrhoea) was unlikely to have been related to the spraying. The main problem was severe skin irritation with burns on the feet. There were 5 workers using low volume sprayers who developed skin lesions on the feet, complicated by scratches and other trauma and infection. All showed delayed healing responses. The degree of skin damage was severe in most of the men. The worker using the high volume knapsack sprayer also developed a rash on his feet, around areas of skin trauma. It was reported as mild.

There were three other spraymen who developed severe skin irritation all as a result of poor working practice. Two were involved in spillages and in one of them there was also splashing of concentrate in the eye causing a severe conjunctivitis but no other effects. This subsided with no sequelae. This man also developed a severe erythematous rash of the trunk and groin and later developed what was described as 'weakness' a few days after the incident, associated with a lowered blood pressure. Recovery was rapid and complete. The third worker was soaked with the 2.0% spray and developed a severe groin irritation. All cases of skin rashes cleared in about 10-14 days with the use of local steroids and antibiotics to combat the supervening infection.

The final medical examinations at one week after spraying had ended showed no abnormalities on routine clinical examination. Chest X-rays were normal and urine was negative for albumen in all workers.

At the end of the two week spraying period those using 'Herbi' applicators had sprayed approximately 12.7 hectares, using 25.4 litres of 'Gramoxone'. The knapsack spraymen covered only 7.3 hectares, using 13.7 litres of 'Gramoxone'. Thus while the rate of application/hectare was roughly the same in the two groups, the 'Herbi' operators were able to cover almost twice the area and therefore use almost twice the amount of 'Gramoxone' at a much higher concentration. The economic implications of this form of spraying are thus obvious and it is not surprising that pressure has developed for low volume application to be cleared for use with paraquat.

DISCUSSION

A number of factors made this trial less satisfactory than planned, but sufficient information was forthcoming to enable a preliminary evaluation of the possible hazard in use of low volume applications of paraquat to be made. The most important consideration is the very high degree of skin contamination that occurred using high concentrations. Although both knapsack and low volume spraying applied equivalent amounts of paraquat per hectare, the low volume technique allowed a much greater area to be covered each day. At the end of the trial, those using the 'Herbi' had applied almost twice the volume of 'Gramoxone' that the knapsack sprayer had used and at a much higher concentration (2% paraquat ion against 0.15% paraquat ion). It is not, therefore, altogether surprising that there was a statistically significant difference between the amount of dermal contamination on those using the 'Herbi' applicator, including its modified

form, and that on the knapsack sprayman after equivalent periods of application. The level of contamination for low volume sprayers was also much higher than that reported by Hogarty³⁶ for knapsack sprayers which did not go above 0.2 mg/25 cm².

This would almost certainly account for the rapid rise in the level of paraquat excreted in the urine of those using the 'Herbi' sprayer when the feet were unprotected. Although it has never been possible, in following cases of human paraquat poisoning, to show a direct correlation between plasma levels of paraquat and urinary excretion, it is certainly true that the level of urinary excretion among these workers matches that obtained after the oral ingestion of the equivalent of 1-2 gm paraquat ion. The urinary levels of paraquat in the 'Herbi' sprayers without foot protection were much higher than those reported by Swan from knapsack spraying or in the author's study reported above. Unfortunately, it was not possible to obtain plasma paraquat estimations on these workers, which might have provided more significant information.

However, of greater importance is the fact that unlike the urinary excretion of paraquat of the knapsack sprayer and those using the 'Herbi' with foot protection, there was a clear indication of rising urinary levels of paraquat among the unprotected workers as the trial progressed, the differences between the groups being statistically highly significant at the end of the second week. This could be interpreted to indicate that there was a rising body burden of paraquat and that the absorption/excretion equilibrium seen in the other workers and noted in other trials with knapsack spraying at high dilutions, was being overcome.

There seems little doubt that a major contributory factor in the increased absorption of paraquat was the marked degree of skin damage caused by the 2% paraquat solution used. Dr. Prasan noted that 5 of the 6 workers using the 'Herbi' applicator without foot protection developed skin damage on the dorsum of the foot, complicated by scratches and other minor trauma.

It needs to be remembered that these findings relate to a supervised trial. In the unsupervised conditions which frequently prevail in the developing countries, the problems with low volume spraying of paraquat by hand would certainly be much worse. There were two spillages in this trial which produced skin problems and it should be noted that the supervisors discouraged the spraymen from washing themselves. In a situation of prolonged or more intensive spraying, the degree of dermal contamination would be greater and carelessness, lack of hygiene, poor protection and other factors would combine to make the problem even greater.

2.5. CONCLUSIONS

The published data reviewed initially in this study, together with the evidence of the author's three investigations reported here, would indicate that neither the formulation of paraquat as commercial preparations nor high volume spraying at concentrations up to 0.5% (1:40 dilution of 'Gramoxone') are likely to pose any significant risk to worker health. Low volume spraying, using high concentrations of paraquat does, however, present a number of problems which will be discussed later.

The importance of the studies of formulation workers and the Malaysian estate sprayers lies in the fact that both groups of workers had experienced a long period of continuous occupational exposure. As was pointed out earlier, such circumstances are very rare for spraymen in temperate climates where spraying is generally seasonal and intermittent. The mean length of exposure in both formulators and spraymen was 5 years and in a number of cases was very much longer (up to 12 or more years). When this is associated with a lower degree of personal protection worn by the Malaysian spraymen, it is reasonable to assume that the degree of exposure was very much higher for these men than for their British or European counterparts. It is therefore important to note that, in spite of this long exposure period, there were no reports of any symptoms from these two groups of workers handling paraquat under very different circumstances that would point to significant systemic absorption, nor indeed were there any complaints of the nature of what has been

termed the 'paraquat-fear syndrome', naively reported by Peoples and his associates²⁶. Furthermore, as far as the spraymen were concerned, a wide range of clinical measurement failed to show any significant variation from the values in unexposed control populations.

The studies reported here indicate that the only clinical manifestations resulting from paraquat exposure under normal use conditions are the local effects on skin and mucous membranes which are well documented and have already been discussed in detail.

The issue of low volume spraying at higher than hitherto recommended concentrations, however, raises very different problems. Exposure to solutions of paraquat at concentrations not much higher than that used in the Thailand trial have since been reported as causing fatalities through percutaneous absorption^{38, 39}, and other cases of death through dermal absorption have been reported in the literature as discussed earlier^{40, 42, 43}. In this particular trial the rising urinary levels of paraquat as spraying continued could be interpreted as evidence of an increasing body burden of paraquat in the spraymen and when this is taken in conjunction with the severe skin responses to the higher spray concentrations, the suggestion cannot be escaped that there was a strong possibility that health could have been seriously endangered had the spraying been allowed to continue for any length of time.

In spite of the economic advantages which low volume/high concentration spraying would bring, there can be no question that the practice would increase the level of risk to the sprayman considerably. Indeed, it is the author's opinion that the degree of risk is far too high to offset any other advantages that the practice might afford. Consequently, low volume/high concentration spraying with paraquat should be actively discouraged wherever it is discovered, especially as the equipment itself has often been modified inexpertly, increasing the level of risk even further.

In conclusion, it is perhaps pertinent to note that the types of study which were set up to investigate the various exposure situations have the advantage of being relatively easy to set up and yet are able to provide valuable information from which a realistic assessment of risk may be obtained. It is suggested that such experimental methods could be adapted easily for studying the risks allegedly posed by other pesticides which have become topics of public concern.

2.5 REFERENCES

1. HOWARD J K, Paraquat: A Review of Worker Exposure in Normal Usage J Soc Occup Med 1980; 30 : 6-11
2. GAGE J C, Some Aspects of the Toxicity of Paraquat Meded Rijksfak Lankd Bouw Wetensch 1969; 34 : 392-400
3. McELIGOTT T F, The Dermal Toxicity of Paraquat: Differences due to Techniques of Application Toxicol Appl Pharmacol 1972; 21 : 361-368
4. HOWARD J K, A Clinical Survey of Paraquat Formulation Workers Brit J Industr Med 1979; 36 : 220-223
5. SWAN A A B, Exposure of Spray Operators to Paraquat Brit J Industr Med 1969; 26 : 322-329
6. HOWARD J K, SABAPATHY N N, WHITEHEAD P ANNE, A Study of the Health of Malaysian Agricultural Workers Occupationally Exposed to Paraquat Brit J Industr Med 1981; 31: 110-115
7. HEARN C E D, KEIR W, Nail Damage in Spray Operators Exposed to Paraquat Brit J Industr Med 1971; 28 : 399-403
8. WITHERS E H, MADDEN J J, LYNCH J B, Paraquat Burns of the Scrotum and Perineum J Tenn Med Ass 1979; 72 : 109
9. BARBER P J, Accidental Vaccination with Paraquat Brit Med J 1971; 2 : 768
10. McDONACH B J, MARTIN J, Paraquat Poisoning in Children Arch Dis Child 1970; 45 : 425-427
11. HOWE D J T, WRIGHT N, The Toxicity of Paraquat and Diquat Proc 18th NZ Wood and Pest Control Conf; 1965 : 105-114
12. SAMMAN P D, JOHNSON E N M, Nail Damage Associated with Handling Paraquat and Diquat Brit Med J 1969; 1 : 818-819

13. BARAN R L, Nail Damage Caused by Weedkillers and Insecticides
Arch Dermatol 1974; 110 : 467
14. DOBBELAERG F, BOUFFIONE J, Leuconychia in Bands due to Paraquat Arch Belg Dermatol 1974; 30 : 283-284
15. CANT J S, LEWIS D R H, Ocular Damage due to Paraquat and Diquat Brit Med J 1968; 2 : 224
16. JOYCE M, Ocular Damage Caused by Paraquat Brit J Ophthalmol 1969; 53 : 688-690
17. PEYRESBLANQUES M J, Ocular Burns Caused by Gramoxone Bull Soc Ophthalmol 1969; 69 : 928
18. FUJITA K, Chemical Burns on the Cornea Caused by Gramoxone Weedkiller Nihon Noson Igakkai Zasshi 1973; 22 : 194-195
19. MIKUNI I, SUZUKI A, A Case of Ocular Erosion by a Herbicide Paraquat Dichloride Ganka Rinsho Iho 1976; 70 : 395-398
20. OISHI S, A Case of Ocular Injury by Parquat Dichloride Sangyo Igaku 1975; 17 : 522
21. SUGIMOTO T, The Occurrence of Ocular Lesions due to Paraquat Dichloride and their Alleviation Sangyo Igaku 1976; 18 : 222-223
22. SINOW U, WEI E, Ocular Toxicity of Paraquat Bull Environ Contamm Toxicol 1973; 9 : 163-168
23. SWAN A A B, Ocular Damage due to Paraquat and Diquat Brit Med J 1968; 2 : 625
24. FITZGERALD G R, BARNIVILLE G, BLACK J, SILKE B, CARMODY M, O'Dwyer W F, Paraquat Poisoning in Agricultural Workers J Irish Med Assoc 1978; 71 : 336-342
25. PEOPLES S A, MADDY K T, RIDDLER L C, Human Health Problems Associated with the Herbicide, Paraquat, in California, 1965 -1976. Los Angeles, Department of Food and Agriculture, California 1977

26. MOURIN K A, Paraquat Poisoning Brit Med J 1967; 4 : 486
27. SWAN A A B, Paraquat Poisoning Brit Med J 1967; 4 : 551
28. GUARDASCIONE V, MAZZELLA DI BOSCO M, On the Occupational Pathology Caused by Paraquat, a Bipyridyl Herbicide Folia Med (Napoli) 1969; 52 : 728-738
29. ELIAHOU H E, ALMOG C, GURA V, IAINA A, The Treatment of Paraquat Poisoning by Haemodialysis Israel J Med Sci 1973; 9 : 459-462
30. Editorial, Paraquat Poisoning Lancet 1976; 1 : 1057
31. MALONE J D G, CARMODY M, KEOGH B, O'DWYER W F, Paraquat Poisoning - A Review of 19 cases J Irish Med Assoc 1971; 64 : 59-68
32. FAO/WHO, Evaluation of Some Pesticide Residues in Food Rome 1972, 469
33. KIMBROUGH R D, GAINES T B, Toxicity of Paraquat to Rats and its Effect on Rat Lungs Toxicol Appl Pharmacol 1970; 17 : 679-690
34. STAIFF D C, COMER S W, ARMSTRONG J F, WOLFE H R, Exposure to the Herbicide Paraquat Bull Environ Contam Toxicol 1975; 14 : 334-340
35. HOGARTY C, Exposure of Spray Operators to Paraquat (Dublin, Institute for Industrial Research and Standards) 1975
36. FELDMANN R J, MAIBACH A M, Percutaneous Penetration of Some Pesticides and Herbicides in Man Toxicol Appl Pharmacol 1974; 28 : 126-132
37. JAROS F, Acute Percutaneous Paraquat Poisoning Lancet 1978; 1 : 275

38. LEVIN P J, KLAFF L J, ROSE A G, FERGUSON A D, Pulmonary Effects of Contact Exposure to Paraquat: A Clinical and Experimental Study Thorax 1979; 34 : 150-160
39. NEWHOUSE M, McEVoy D, ROSENTHAL D, Percutaneous Paraquat Absorption Arch Dermatol 1978; 114 : 1516-1519
40. WESTON J T, DIXON M G, Untoward Effects of Exogenous Inhalants on the Lung J Forensic Sci 1972; 17 : 199-279
41. ONGOM V L, OWOR R, TOMUSANGE E T, Paraquat ('Gramoxone') used as a Pediculocide In: The Uses and Abuses of Drugs and Chemicals in Tropical Africa Bagshore A F (Ed.) Nairobi, East Africa Literature Bureau 1974, 229-233
42. BINNS C W, A Deadly Cure for Lice Papua N G Med J 1976; 19 : 105-107
43. McDONAGH B J, MARTIN J, Paraquat Poisoning in Children Arch Dis Child 1970; 45 : 425-427
44. GERVAIS P, DIAMANT-BERGER O, BESCOL-LIVERSAC J, GUILLAM C, GUYON F, Problemes Medico-legaux et Medico-sociaux de l'Intoxication Aigue par les Herbicides du Groupe du Paraquat Arch Mal Prof Med Trav Sec Soc 1975; 36 : 19-36
45. CONSO F, Intoxication Aigue par le Paraquat: Experience des Centres Anti-Poisons Francais Bull Med Leg Toxicol 1978; 21 : 117-120
46. GARNIER R, CONSO F, EFTHYMIOU M L, FOURNIER E, Toxicity of Paraquat by Inhalation. Arch Mal Prof 1980; 41 : 21-22
47. GEORGE M, HEDWORTH-WHITTY R B, Non fatal lung disease due to inhalation of rebulised paraquat. Brit Med J 1980; 280 : 902
48. ADAM R J, Non fatal disease due to inhalation of rebulised paraquat. Brit Med J 1980; 280 : 1120-1121

49. CONNING D M, FLETCHER K, SWAN A A B, Paraquat and Related Bipyridyles Brit Med Bull 1969; 25 : 245-249
50. SEIDENFELD J J, WYCOTT D, ZAVALA D C, RICHESSEN H B, Paraquat Lung Injury in Rabbits Brit J Industr Med 1978; 35 : 245-257
51. HATCH T F, GROSS P, Pulmonary Deposition and Retention of Aerosols New York, Academic Press 1964
52. LITCHFIELD M H, DANIEL J W, LONGSHAW S, The Tissue Distribution of the Bipyridylum Herbicides, Diquat and Paraquat, in Rats and Mice Toxicology 1973; 1 : 155-165
53. MURPHY S D, Pesticides In Toxicology: The Basic Science of Poisons (Cassarett L J, Doull J, Eds.) New York, MacMillan 1975; 439
54. WORLD HEALTH ORGANISATION, Standard Protocol for the Survey of Exposure to Organophosphorus Pesticides in Agriculture (VBC/75.9) Geneva WHO 1975
55. LEVITT T, Determination of Paraquat in Clinical Practice Using Radioimmunoassay Proc Analyt Div Chem Soc Feb 1979; 72-76
56. CALDERBANK A, YUEN S H, An Ion-exchange Method for Determining Paraquat Residues in Food Crops Analyst 1965; 90 : 99-106
57. DOCUMENTA GEIGY, Scientific Tables (Diem K, Kentner C, Eds.) Basle, Ciba-Geigy, 7th edition 1972
58. CHESTER G, WOOLLEN B H, A Study of the Occupational Exposure of Malaysian Plantation Workers to Paraquat Brit J Industr Med 1981; (in the press)
59. ARNOLD A C, Droplet Spectra for the Twenty most Commonly used Hydraulic Nozzles London, British Crop Protection Council 1979

60. MILLEDGE J S, Vital Capacity and Forced Expiratory Volumes in one Second in South Indian Men Ind J Chest Dis 1965; I : 97-102
61. DA COSTA J L, GOH B K, Prediction Nomograms for Lung Function Measurements in Adult Chinese Sing Med J 1971; 12 : 193-198
62. ZEE K O, CHEW P K, Ventilatory Function in Normal Industrial Malay Workers in Singapore Sing Med J 1976; 17 : 242-247
63. BERGLUND E, BIRATH G, BJURE J, GRIMBY G, KJELLMER I, SANGVIST L, Spirometric Studies in Normal Subjects Between 7 and 70 Years of Age Acta Med Scand 1963; 173 : 185-191
64. OGILVIE C M, FORSTER R E, BLAKEMORE W I, MORTON J W, A Standardised Breath Holding Technique for the Clinical Measurements of the Diffusing Capacity of the Lung for Carbon Monoxide J Clin Invest 1957; 36 : 1-7
65. DALY J J, ROE J W, Serial Measurements of the Pulmonary Diffusing Capacity for Carbon Monoxide in a Group of Men Employed in Industry Thorax 1962; 17 : 298-302
66. NEWMAN F, SMALLING B F, THOMSON M L, Effect of Exercise, Body and Lung Size on Carbon Monoxide Diffusion in Athletes and Non-athletes J Appl Physiol 1962; 17 : 649-655
67. LAUTENSCHLAGER J, GRABENSEC B, POTGIN W, Isolierte Aplastische Anämie nach Paraquatvergiftung Blut 1974; 28 : 221
68. BULLIVANT C M, Accidental Poisoning by Paraquat: Report of Two Cases in Man Brit Med J 1966; i : 1272-3

APPENDIX 2.1: REGRESSION EQUATIONS FOR

CLINICAL MEASUREMENTS

Regression equations fitted involved eight independent variables denoted by x_1, x_2, \dots, x_8 where;

$x_1 = 1$ for a sprayer (0 for a general worker or factory worker)	$x_2 = 1$ for a general worker (0 for a sprayer or factory worker)	$x_3 = 1$ for Indian (0 for Malay or Chinese)	$x_4 = 1$ for Malay (0 for Indian or Chinese)
$x_5 = 1$ for smoker (0 for non-smoker)	$x_6 = \text{No of cigarettes smoked}$ a day	$x_7 = \text{Age (years)}$	$x_8 = \text{Height (cm)}$

Derived regression equations are set out as follows:

									% Fit
FVC	= -4.448	+ 0.139x ₁	- 0.187x ₂	- 0.346x ₃	- 0.185x ₄	+ 0.434x ₅	- 0.0115x ₆	- 0.0156x ₇	+ 0.0507x ₈ 39
FEV ₁	= -3.837	- 0.141x ₁	- 0.140x ₂	- 0.413x ₃	- 0.201x ₄	- 0.395x ₅	- 0.0160x ₆	- 0.0218x ₇	+ 0.0461x ₈ 47
FEV%	= 88.53	+ 1.04x ₁	- 0.70x ₂	- 3.78x ₃	- 1.93x ₄	- 0.23x ₅	- 0.193x ₆	- 0.254x ₇	- 0.062x ₈ 20
DCO	= 5.16	- 0.63x ₁	- 0.22x ₂	- 1.44x ₃	- 0.03x ₄	- 0.99x ₅	- 0.030x ₆	- 0.105x ₇	+ 0.063x ₈ 44
Hb	= 13.04	- 0.34x ₁	- 0.33x ₂	- 0.38x ₃	- 0.57x ₄	- 0.36x ₅	- 0.029x ₆	- 0.003x ₇	+ 0.007x ₈ 10
PCV	= 37.61	- 1.90x ₁	- 0.18x ₂	- 0.24x ₃	- 1.15x ₄	- 1.18x ₅	- 0.082x ₆	- 0.014x ₇	+ 0.032x ₈ 14
RBC	= 5.599	- 0.262x ₁	- 0.028x ₂	- 0.148x ₃	- 0.044x ₄	- 0.267x ₅	- 0.0105x ₆	- 0.0084x ₇	+ 0.016x ₈ 15
MCV	= 69.85	+ 0.43x ₁	- 0.44x ₂	- 1.59x ₃	- 2.53x ₄	- 6.47x ₅	- 0.322x ₆	- 0.109x ₇	+ 0.011x ₈ 24
MCH	= 24.11	- 0.71x ₁	- 0.71x ₂	- 1.28x ₃	- 1.09x ₄	- 2.00x ₅	- 0.110x ₆	- 0.039x ₇	- 0.0003x ₈ 20
log ₁₀ WBC	= 4.2115	- 0.0186x ₁	- 0.0771x ₂	+ 0.0442x ₃	- 0.0065x ₄	+ 0.0533x ₅	- 0.00416x ₆	- 0.00225x ₇	- 0.00133x ₈ 27
log ₁₀ AST	= 1.9974	- 0.0300x ₁	- 0.0596x ₂	- 0.0859x ₃	- 0.0390x ₄	- 0.0606x ₅	- 0.00299x ₆	- 0.00061x ₇	- 0.00414x ₈ 9
log ₁₀ ALT	= 0.3417	- 0.4302x ₁	- 0.3937x ₂	- 0.2790x ₃	- 0.1052x ₄	- 0.1726x ₅	- 0.00679x ₆	- 0.00344x ₇	+ 0.00379x ₈ 57
log ₁₀ ALKP	= 2.0994	- 0.0889x ₁	- 0.1366x ₂	+ 0.0336x ₃	- 0.0568x ₄	- 0.1265x ₅	- 0.00338x ₆	- 0.00185x ₇	- 0.00308x ₈ 34
log ₁₀ CREAT	= 0.5176	- 0.0383x ₁	- 0.0994x ₂	+ 0.0632x ₃	- 0.0057x ₄	+ 0.0479x ₅	- 0.00163x ₆	- 0.00031x ₇	- 0.00294x ₈ 23
log ₁₀ BUN	= 0.6444	- 0.0757x ₁	- 0.0839x ₂	- 0.0145x ₃	- 0.0118x ₄	+ 0.0279x ₅	- 0.00180x ₆	- 0.00133x ₇	+ 0.00253x ₈ 23

APPENDIX 2.2: MALAYSIAN SPRAY WORKER STUDY - INDEPENDENT VARIABLES

OBS	x ₁ SPRAYER	x ₂ GEN_WORK	x ₃ INDIAN	x ₄ MALAY	x ₅ SMOKER	x ₆ CIGS	x ₇ AGE	x ₈ HEIGHT
1	1	0	0	1	1	10	55	61.5
2	1	0	0	1	1	5	25	63.5
3	0	1	1	0	1	7	41	64.5
4	0	1	0	0	1	25	23	68.5
5	1	0	0	1	0	0	43	63.0
6	0	1	1	0	1	10	54	64.0
7	1	0	1	0	1	10	25	67.5
8	1	0	1	0	1	0	28	68.0
9	1	0	1	0	0	3	32	66.0
10	1	0	1	0	1	0	43	61.0
11	1	0	0	1	0	10	19	62.0
12	1	0	1	0	1	40	24	65.0
13	1	0	1	0	0	0	44	64.0
14	1	0	1	0	1	10	28	66.0
15	0	1	1	1	0	0	17	65.0
16	0	1	1	1	1	10	18	62.0
17	1	0	1	0	1	0	19	62.5
18	0	1	0	0	1	6	24	64.5
19	1	0	0	0	1	10	25	61.0
20	1	1	0	0	1	0	47	61.0
21	1	1	0	0	0	0	16	63.5
22	0	0	1	1	0	0	29	60.0
23	1	1	1	0	0	0	53	64.0
24	1	1	0	0	1	20	30	64.0
25	1	1	1	0	1	20	51	67.5
26	2	0	0	0	0	0	38	65.0
27	0	0	1	1	0	0	59	63.0
28	0	0	1	1	0	0	38	65.0
29	0	0	1	1	0	15	37	64.0
30	0	0	1	1	0	10	34	65.0
31	0	0	1	1	1	15	45	63.0
32	0	0	1	1	1	0	34	64.0
33	0	0	1	1	0	0	30	61.5
34	0	0	1	1	0	0	29	59.5
35	0	0	1	1	0	15	25	67.5
36	0	0	1	1	0	12	49	67.0
37	0	0	1	1	0	15	32	66.0
38	0	0	1	1	0	20	45	66.0
39	0	0	1	1	1	20	35	63.0
40	0	0	1	1	1	0	45	66.5
41	0	1	0	1	1	15	32	61.5
42	0	1	0	1	1	12	41	63.0
43	0	1	1	0	1	15	28	62.0
44	0	1	1	0	1	12	24	68.0
45	0	1	1	0	1	15	18	66.0
46	0	1	1	0	0	0	24	60.5
47	0	1	1	0	0	0	46	68.0
48	0	1	1	0	0	20	30	62.0
49	0	1	1	0	0	20	43	63.5
50	0	1	1	0	1	0	19	63.0
51	0	0	1	0	1	6	22	67.0
52	0	0	1	0	1	12	21	61.0
53	0	0	0	0	1	4	21	63.0
54	0	0	0	0	1	3	45	60.5
55	0	0	0	0	1	40	53	62.5
56	0	0	0	0	1	7	45	63.5
57	0	0	0	0	1	10	21	63.0
58	0	0	0	0	1	18	19	64.0
59	0	0	0	0	1	0	19	66.0
60	0	0	0	0	1	15	32	62.0
61	0	0	0	0	1	12	19	62.5
62	0	0	0	0	1	0	30	64.5
63	0	0	0	0	1	12	24	68.0
64	0	0	0	0	1	0	19	64.0
65	0	0	0	0	1	12	43	64.0
66	0	0	0	0	1	8	27	61.0
67	0	0	0	0	1	6	25	64.5
68	0	0	0	0	1	15	28	60.5
69	0	0	0	0	1	7	41	63.5
70	0	0	0	0	1	0	18	61.5
71	0	0	0	0	1	12	40	67.0
72	0	0	0	0	1	8	28	61.5
73	0	0	0	0	1	0	40	67.0
74	0	0	0	0	1	15	28	61.5

APPENDIX 2.3: MALAYSIAN SPRAY WORKER STUDY - RESPIRATORY

FUNCTION VALUES

OBS	FVC	FEV1	FEV1_PC	DCO
1	2.68	2.35	87.6	21.93
2	3.84	3.48	90.6	28.68
3	3.62	3.44	95.0	16.26
4	3.27	3.12	95.4	32.54
5	3.11	2.71	87.1	22.57
6	3.05	2.05	67.2	13.37
7	3.62	3.46	95.5	28.56
8	4.00	3.08	77.0	25.25
9	3.14	2.81	89.4	32.51
10	2.64	2.22	84.0	24.79
11	3.76	3.35	89.0	31.09
12	4.24	3.80	89.6	33.45
13	3.17	2.61	82.3	23.90
14	2.66	2.47	92.8	37.48
15	3.41	2.76	80.9	31.13
16	.	.	.	28.46
17	3.43	3.41	99.4	42.43
18	3.24	3.05	94.1	45.19
19	2.65	2.25	84.9	27.77
20	2.14	1.92	89.7	20.85
21	3.28	3.20	97.5	32.89
22	2.64	2.37	89.7	25.52
23	3.25	2.73	84.0	26.04
24	3.94	3.10	78.6	25.03
25	3.75	2.90	77.3	21.16
26	2.44	2.27	93.0	29.48
27	3.42	2.74	80.1	38.77
28	3.39	3.37	99.4	36.69
29	3.12	2.41	77.2	37.43
30	3.53	2.81	79.6	36.60
31	2.63	2.27	86.3	24.95
32	2.89	2.52	87.1	.
33	3.21	2.69	83.8	28.55
34	2.88	2.26	78.4	26.90
35	4.64	3.84	82.7	35.53
36	3.65	3.27	89.5	36.58
37	2.64	2.44	92.0	.
38	4.91	4.12	83.9	.
39	2.71	2.44	90.0	.
40	4.72	3.63	76.8	.
41	3.80	3.01	79.2	25.30
42	3.35	3.63	95.5	39.71
43	2.81	2.43	86.4	36.50
44	4.09	3.50	80.6	33.41
45	4.40	3.80	86.3	27.38
46	.	.	.	36.61
47	2.39	2.70	93.4	34.72
48	4.30	4.59	95.6	41.18
49	3.00	2.20	73.3	22.84
50	3.74	3.15	84.2	32.22
51	2.56	2.49	97.2	23.42
52	2.86	2.31	80.7	43.55
53	3.45	3.22	93.3	27.65
54	3.20	3.04	95.0	28.91
55	3.44	3.18	92.4	31.36
56	3.23	2.99	92.5	29.80
57	3.11	2.49	83.0	34.13
58	3.02	2.21	73.1	22.44
59	3.87	3.12	80.6	32.54
60	3.80	3.22	84.7	37.50
61	3.43	3.38	93.5	42.68
62	2.61	1.56	59.7	26.78
63	3.54	3.29	92.9	30.29
64	3.54	3.10	87.5	34.91
65	4.00	3.83	95.7	28.26
66	3.51	3.24	92.3	29.76
67	3.01	2.38	79.0	23.51
68	3.34	2.80	83.8	41.17
69	3.38	3.18	94.0	36.59
70	2.80	2.57	91.7	38.46
71	3.75	3.08	82.1	32.68
72	2.50	2.36	94.4	33.58
73	3.51	3.35	95.1	29.80
74	2.26	2.23	98.6	28.23

APPENDIX 2.4: MALAYSIAN SPRAY WORKER STUDY - HAEMATOLOGY VALUES

OBS	HB	PCV	RBC	MCV	MCH	WBC
1	15.5	44.7	5.69	78	27.2	5500
2	14.2	43.2	5.28	81	26.8	7100
3	14.7	41.4	4.79	86	30.6	9000
4	14.5	41.5	5.12	81	28.5	8300
5	14.3	42.2	5.10	82	28.0	9400
6
7	14.4	42.3	6.05	69	23.8	7200
8	16.6	45.6	5.56	82	29.8	12000
9	14.0	43.2	5.64	76	24.8	7400
10	12.7	37.5	4.10	91	30.9	8600
11	15.0	41.4	5.04	82	29.7	7500
12	13.1	37.6	4.89	76	26.7	9600
13	13.4	38.0	5.25	72	25.5	5200
14	16.1	43.3	5.62	77	28.6	6200
15	13.8	39.7	5.25	75	26.2	8000
16
17	14.3	42.1	5.47	76	26.1	14800
18	13.9	39.5	4.81	82	28.8	7800
19	13.0	38.4	4.55	84	28.5	10900
20	13.7	38.5	4.81	80	28.4	10000
21	13.0	36.9	5.14	71	25.2	7200
22	16.2	41.9	5.36	78	30.2	5400
23	16.3	48.2	5.74	83	28.3	5400
24	16.5	45.7	5.51	82	29.9	10400
25	12.3	34.8	4.33	80	28.4	7500
26	13.4	37.7	4.38	77	27.4	6700
27	14.0	42.3	5.27	80	26.5	7700
28	13.8	40.4	4.94	81	27.9	5900
29	15.5	45.0	5.75	78	26.9	4700
30	13.1	37.6	5.10	73	25.6	8100
31	15.0	40.7	5.29	80	28.3	8700
32	14.3	40.3	5.54	73	25.8	7800
33	13.4	41.7	6.89	60	19.4	6900
34	14.1	40.7	5.24	77	26.9	13300
35	15.0	45.4	6.08	74	24.6	7000
36	14.1	40.8	5.55	73	25.4	7600
37	13.4	42.3	4.97	85	26.9	6400
38	14.3	46.3	6.39	72	22.3	6200
39	16.7	48.2	6.00	80	27.8	6800
40	14.9	43.3	5.61	77	26.5	6500
41	14.0	40.4	5.01	80	27.9	14900
42	14.6	43.8	5.73	75	25.4	5800
43	15.5	40.7	5.31	76	24.1	6400
44	14.5	43.0	5.22	82	27.1	5600
45
46	12.3	35.8	4.39	81	28.0	8800
47	13.7	41.8	5.41	77	25.4	8200
48	16.9	47.8	5.84	81	28.9	8900
49	12.7	37.5	4.34	86	29.2	9000
50	15.6	44.3	5.69	77	27.4	11300
51	14.2	41.1	4.94	83	28.7	8000
52	14.0	42.0	5.08	82	27.5	9800
53	14.3	41.8	5.40	77	26.4	7900
54	14.5	43.2	5.31	81	27.3	10000
55	14.2	41.3	5.37	76	26.4	10200
56	17.9	52.5	6.00	87	29.8	7500
57	11.6	36.2	5.66	63	20.4	5300
58	13.6	39.9	4.74	84	28.6	10700
59	14.9	44.8	5.64	79	26.4	11600
60	14.3	41.3	5.65	73	25.3	3200
61	15.6	45.7	5.79	78	26.9	8600
62	15.8	46.7	5.83	80	27.1	10300
63	14.3	43.1	5.02	85	28.4	7300
64	12.2	39.1	6.41	61	19.0	11600
65
66
67	15.0	41.3	5.22	79	28.7	9600
68
69	14.5	42.1	5.19	81	27.9	10500
70	16.7	51.5	5.90	87	28.3	8400
71	14.0	40.1	5.10	78	27.4	7500
72	14.7	43.7	5.51	79	26.6	9600
73	13.5	39.5	4.72	83	28.6	8500
74	15.3	47.4	5.60	84	27.3	7700

APPENDIX 2.5: MALAYSIAN SPRAY WORKER STUDY - LIVER FUNCTION VALUES

OBS	AST	ALT	ALKP	CREAT	BUN
1	20	31	22	0.9	10
2	22	25	33	0.9	10
3	25	31	23	0.9	11
4	13	15	20	1.0	11
5	22	36	40	0.7	3
6
7	16	41	20	1.1	9
8	20	78	23	1.3	13
9	18	72	23	1.2	10
10	27	16	18	1.2	7
11	20	35	41	1.2	8
12	18	53	72	1.0	10
13	30	141	32	1.2	15
14	39	196	33	1.1	11
15	24	92	13	1.2	11
16
17	23	47	29	2.2	11
18	17	25	20	1.4	14
19	21	66	30	1.1	15
20	15	23	32	1.0	15
21	15	18	26	0.8	7
22	37	91	29	1.0	7
23	24	35	48	1.3	9
24	32	78	35	1.2	12
25	15	27	23	0.8	13
26	10	32	26	1.0	12
27	21	61	19	1.0	13
28	10	23	25	1.1	13
29	18	51	31	1.0	10
30	16	46	28	0.9	15
31	24	72	23	1.1	13
32	6	23	31	0.9	12
33	30	52	25	0.7	9
34	24	25	21	0.8	12
35	36	41	27	0.9	11
36	19	25	30	0.9	7
37	15	33	21	1.0	15
38	24	41	21	0.6	10
39	21	36	27	0.5	15
40	9	31	25	0.6	11
41	17	26	16	2.4	19
42	21	25	22	0.8	9
43	13	18	31	1.1	10
44	14	22	20	1.3	11
45	28	28	20	1.2	19
46	30	54	20	1.2	13
47	15	20	33	1.0	12
48	24	41	27	0.7	13
49	31	92	33	1.2	19
50	31	41	30	0.6	8
51	19	36	25	0.6	8
52	21	13	41	0.9	14
53	21	6	33	1.3	16
54	14	7	39	1.1	20
55	17	5	30	1.3	13
56	31	27	39	1.3	14
57	21	9	26	1.3	18
58	24	15	33	1.6	10
59	21	14	44	1.3	14
60	19	8	33	0.9	14
61	19	6	48	1.4	12
62	24	10	25	1.1	14
63	19	13	36	1.1	12
64	29	16	39	1.3	12
65
66
67	31	35	31	0.7	14
68
69	24	13	28	1.2	13
70	24	12	41	1.1	9
71	19	26	23	1.4	18
72	31	19	65	1.1	12
73	13	19	16	1.0	13
74	29	30	45	1.2	12

SECTION 3

THE MISUSE OF PARAQUAT: THE PROBLEM OF
ACCIDENTAL AND INTENTIONAL POISONING

3 THE MISUSE OF PARAQUAT: THE PROBLEM OF ACCIDENTAL AND INTENTIONAL
POISONING

3.1 THE EXTENT OF THE PROBLEM

It is not possible to gain an accurate picture of the size of the problem of paraquat poisoning on a world-wide basis. Few countries keep sufficiently accurate statistics and even where good recording systems exist they are often not sufficiently detailed to allow deaths from paraquat poisoning to be isolated from those caused by other agricultural chemicals. The general literature is also of little help in this respect as, although there have been a large number of reports of single fatal cases or small groups of cases, there have been remarkably few attempts to collate data from several sources or publish large series. Further, cases of survival from paraquat poisoning have been poorly documented and consequently the overall incidence of poisoning is difficult to define accurately.

The problem is compounded by the fact that frequently authors fail to make any distinction between accidental and deliberate poisoning in their reporting of cases and on other occasions purposive self-poisoning is reported as 'accidental', thus giving a very distorted picture. The following discussion, although limited by the quantity and quality of the data, will endeavour to provide some idea of the situation world-wide and also the relative importance of accidental and deliberate poisoning with paraquat.

Park and his colleagues¹ published a series of 31 cases treated in

Edinburgh and more recently Fitzgerald and his colleagues² have reviewed 136 cases of poisoning occurring in Ireland, between 1967 and 1977. This is the largest published series so far in the world literature and probably accounts for virtually all of the paraquat poisoning cases in the Irish Republic in this period. He and his colleagues have also published a short series of 13 cases of long-term follow-up after recovery from paraquat poisoning³. Carson and Carson have analysed 26 fatal and 7 non-fatal cases occurring in Northern Ireland between 1967 and 1975^{3a} and note that the incidence of paraquat poisoning has been proportionately higher in Ireland than elsewhere. The present author has published a series of 68 cases of poisoning occurring in Britain between 1975 and 1977⁴, but these were selected cases and the series is certainly incomplete as far as the total number of poisonings is concerned in these years. Wright and his co-workers⁵ have also published a series of seventy cases from the Birmingham area relating the severity of poisoning to urinary paraquat excretion. From France Mme Conso has reviewed the experience of the French Poison Control Centres between 1970 and 1977⁶, but again her series is admittedly incomplete as not all cases were reported to the Poison Centres. Fletcher⁷ attempted to record all the published cases to 1974, but while giving some evidence of geographical distribution and the relative incidence of accidental and deliberate poisonings, such a review does not provide any real idea of the actual incidence of poisoning. There have been a number of other reports and reviews, but most of these collected cases have only examined one aspect of the problem, namely intentional poisoning, and have not addressed themselves to the parallel problem of accidental poisoning.

3.1.1 ACCIDENTAL POISONING

There are very few accurate statistics from which a picture can be built up of the world-wide incidence of accidental paraquat poisoning. The United Kingdom probably has the most complete figures currently available, derived from both official statistics and the record of paraquat 'incidents' maintained by ICI Ltd. The total number of accidental deaths from paraquat is small (table 3.1) and it is worth noting that since the introduction of better labelling in 1972, together with an education programme designed to warn farmers and others of the dangers of decanting agricultural concentrates into other containers (frequently soft drinks bottles) and the restriction of the sale of such concentrates to farmers and professional horticulturists, the number of deaths from accidental ingestion of paraquat has fallen quite dramatically. Further, the problem of accidental poisoning is restricted to the agricultural concentrates (Gramoxone, etc) and there are no records of any fatalities from accidents with the granular retail products. The difference between the pre-and post-1972 figures are just outside the limits of statistical significance ($t = 1.86$; $df = 4$; $P < 0.1$), but both the total sample and the annual figures are very small.

It is encouraging, however, to note the relatively small number of children involved in such accidents, a fact to which Fraser has recently drawn attention⁸. The four cases of fatal childhood poisonings between 1968 and 1972 represent 2.7 per cent of the total of 148 cases of fatal accidental child poisonings occurring in that period from all causes. The two cases that

TABLE 3.1 ACCIDENTAL POISONING DEATHS FROM
PARAQUAT IN UK: 1968-1977

	Adults	Children*	Total	Mean/Year
1968-72	19	4	23	4.6
1973-77	12	2	14	2.8
Totals	31	6	37	3.7

* Source: Fraser N C, Brit Med J 1980; 280 : 1595-98

occurred between 1973 and 1977 are 1.9 per cent of the 105 fatal accidental poisonings of children in these years. However, the problem of distinguishing accidents from attempts at self-harm is difficult even in children and it is highly probable that some reported childhood 'accidents' are misrepresentations.

Evidence of the size of the problem elsewhere is hard to obtain. The author has examined the detailed figures for Japan collected by ICI (Japan) Ltd for the years 1975 and 1976 and in this period only three cases of paraquat poisoning were reported as accidental, all others being deliberate. The official Government statistics, however, differ from these, being considerably higher. The figures are set out in table 3.2. Total pesticide accidents are set alongside for comparison. It is possible that these figures represent under-reporting, but there are factors in the Japanese situation that, while tending to make intentional poisoning easier, militate against accidents. Of these undoubtedly the most important is the size of container used for the agricultural concentrate 'Gramoxone'. Because the great majority of Japanese farmers cultivate a very small area (generally no more than a small holding) there has been little demand for large quantities of concentrate, merely sufficient for a single application at the beginning of the growing season. 'Gramoxone' was thus marketed for commercial use, until very recently, in 100 ml plastic bottles and there was thus little likelihood of material being decanted into smaller unlabelled containers (the main cause of accidental poisoning). The small size of pack did, however, make ingestion with suicidal intent much easier. The recent change to a 1 litre container as part of a campaign to reduce suicidal use of paraquat may alter the situation.

TABLE 3.2 ACCIDENTAL PARAQUAT POISONING

IN JAPAN: 1971-1977

	Accidental Paraquat Poisoning			All Accidental Pesticide Poisonings		
	Fatal	Non-Fatal	Total	Fatal	Non-Fatal	Total
1971	6	1	7	28	9	37
1972	3	-	3	23	37	60
1973	2	1	3	12	8	20
1974	1	1	2	10	8	18
1975	6	1	7	14	28	42
1976	2	2	4	12	19	31
1977	6	-	6	22	11	33

Source: Annual Report of Japanese Ministry of Agriculture,
Food and Fisheries, Tokyo 1978.

Accidental deaths have been reported from many other countries^{9,10}, but occasional incident reports do not provide any real indication of overall frequency. Furthermore, the looseness of terminology in many instances makes it difficult to decide whether a particular incident was genuinely accidental or deliberate. The general impression, however, is that accidental paraquat poisoning does not present a major problem and that on this ground alone, there is no reason for banning the product as too dangerous as some have proposed¹¹.

3.1.2 DELIBERATE SELF-POISONING

Once again, it is not possible to estimate the size of the problem throughout the world. It is known that a number of countries, such as the United States, do not have a problem with paraquat poisoning even though large amounts may be used in agriculture. The reasons for this probably relate to the patterns of use and general availability of the product as well as possible cultural preferences in suicide methods. On the other hand, a number of countries such as the United Kingdom, Eire and Japan do have significant numbers of deliberate self-poisonings each year.

The most accurate figures for the annual incidence of deliberate paraquat deaths probably come from Japan. The incidence of suicide from all causes is high in Japan, which reflects the fact that suicide has been rooted in Japanese culture from the days of ritual seppuku by the samurai as a face-saving and honourable form of death. According to Japanese government

statistics, the annual suicide rate in Japan is about 15,000 to 20,000 in a population of approximately 114 million.

The great majority of suicides are caused by mechanical means (jumping from tall buildings, falling in front of trains etc.) and self-poisoning accounts for a relatively small percentage of the total deaths. Table 3.3 indicates the number of deliberate self-poisonings with pesticides in Japan between 1970 and 1977, the last year for which the author has been able to obtain complete figures for all pesticides. Total numbers have shown a steady decline, but both the real numbers and the proportion of paraquat poisonings show a marked increase. This trend has continued beyond 1977 through the years 1978 and 1979, by which time the number of paraquat poisonings had reached 110 per annum.

The equivalent figures for two other commonly used pesticides, parathion and malathion (both organo-phosphorus insecticides) are included to provide a comparison. It is worth noting that the dramatic decline in deliberate parathion self-poisoning was the direct result of government action. This insecticide was re-classified in 1972 as tokutei dokubutsu, that is 'special poison', which resulted in the very stringent regulations associated with this class of compounds being applied to parathion. As a result the possession and use of this pesticide was so severely restricted that it was effectively removed from the market and from general use within a very short time.

The other important point which emerges from these figures is the very high mortality associated with paraquat poisoning. Table 3.4

TABLE 3.3 DELIBERATE SELF-POISONING WITH
PESTICIDES IN JAPAN: 1970-1977

	POISONING CASES							
	Paraquat		Parathion		Malathion		All Pesticides	
	Non-Fatal	Fatal	Non-Fatal	Fatal	Non-Fatal	Fatal	Non-Fatal	Fatal
1970	-	-	113	4	62	13	725	94
1971	40	2	83	3	66	9	574	110
1972	50	4	54	1	50	16	545	123
1973	36	6	41	3	47	10	423	118
1974	48	3	30	5	30	12	396	108
1975	82	1	6	-	30	13	423	103
1976	82	6	21	1	nr	nr	405	108
1977	101	8	11	-	nr	nr	410	103

nr : not reported separately

Source: Annual Report of Japanese Ministry of Agriculture
Food and Fisheries, Tokyo 1978.

TABLE 3.4 MORTALITY FROM DELIBERATE SELF-POISONING
WITH PESTICIDES IN JAPAN: 1971-1977

Year	Mortality (%)	
	Paraquat	All Other Pesticides
1971	95.2	83.2
1972	92.6	80.6
1973	85.7	77.6
1974	94.1	76.8
1975	98.8	76.9
1976	93.2	68.4
1977	92.7	69.3

The differences in mortality rates are highly significant
($t = 6.93$; $df = 6$; $P < 0.0005$)

compares the mortality from paraquat ingestion with that for all other pesticide poisoning in Japan for the years 1971-1977. All pesticide poisonings are associated with a high mortality, no doubt to be associated with the large amounts ingested, but the mortality from paraquat poisoning is significantly higher than that for all other pesticides ($t = 6.93$; $df = 6$; $P < 0.0005$). As will be discussed later, this high mortality is almost certainly linked to the fact that only the 20% agricultural concentrate ('Gramoxone') is available in Japan and also that it is relatively easy to obtain. Consequently, a large amount of paraquat may be ingested easily with fatal results.

High mortalities are also to be found in other countries where only 'Gramoxone' and similar high concentration formulations are available and where suicide rates are higher. Eastern Malaysia and Western Samoa have shown similar patterns of mortality to Japan (J. K. Howard 1977, unpublished ICI Internal Report). In Western Samoa there are about 25 or more cases of paraquat self-poisoning every year in a population of only 153,000. The mortality approaches 90 per cent and what is particularly tragic about many of these cases is that they involve young people as the result of relatively minor domestic upsets. What set off as a mere gesture or a 'cry for help' turns into an irreversible tragedy (J. K. Howard, unpublished observations).

The size of the problem in the United Kingdom in absolute terms is much smaller than Japan, although the total number of both fatal and non-fatal poisonings is not known. It is, however, possible to provide a reasonable estimate of numbers. It is known that the National Poisons Information Service deals with

approximately 300 calls per year relating to paraquat poisoning (J. A. Vale 1979, personal communication). A large proportion of these are 'false alarms', but it is estimated that about 70-80 of these do represent genuine paraquat self-poisonings. Many of them will be trivial, little more than 'gestures', using very small amounts of retail granular formulations such as 'Weedol'. The mortality from these attempts may be estimated approximately from the Registrar General's statistics, although changes in classification make it difficult to compare year with year. In 1979, however, there were 31 deaths from self-administration of 'farming and gardening preparations, not plant foods or fertilizers' (Class E863) and it is likely that most, if not all, these deaths were due to paraquat. The total suicide deaths for 1979 were 4195, so that paraquat deaths account for well under 1 per cent of the total. According to ICI Ltd records, the number of paraquat fatalities for 1980 was about 37 (L.L. Smith 1981, personal communication).

It will be apparent that the mortality in the United Kingdom appears to be very much lower than in other countries. An estimate from the combination of the Registrar General's figures and the total cases reported both to ICI Ltd and the National Poisons Information Service would suggest a mortality of about 40 to 50 per cent. This is in broad agreement with other estimates that put mortality in the region of 60 per cent^{1,2,4,9,12}. There would appear to be two main factors which probably account for this lower mortality compared with Japan. The first is that the liquid agricultural concentrates containing 20% paraquat ion

(e.g. 'Gramoxone') are less easily obtained by the general public in the UK than they are, say, in Japan. They are properly only available to bona fide farmers and horticulturists and the 'poisons book' should be signed on purchase. Secondly, there is an increasing tendency by would be suicides to use the retail granular preparations such as 'Weedol' for deliberate self-poisoning. These have a low concentration of paraquat ion which means that a large quantity of a highly unpalatable material must be ingested before it would prove fatal. The past few years have seen a marked shift to the use of such easily obtained formulations with a consequent reduction in mortality (J. A. Vale 1979, personal communication). The problem of deliberate self-poisoning thus does not appear to be a major problem in the United Kingdom in terms of total numbers.

Small series of cases from a number of other countries have been published. The Swiss Poison Control Centre dealt with 14 cases of paraquat ingestion in the period 1966-1975¹³; the Dutch Poison Control Centre has reported on 15 cases of deliberate ingestion from 1964 to 1974¹⁴ and the French Poison Control Centre on 45 cases of poisoning by ingestion, of which 20 cases were deliberate⁶. Suicides in Malaysia have only been analysed up to 1972¹⁵, but between 1968 and 1972 there had been 82 cases of deliberate self-poisoning with herbicides of which 56 were due to paraquat. There were 61 deaths, most of which may be presumed to have been from paraquat ingestion although this is not stated. It is recorded, however, that mortality was very high. The total recorded cases of intentional poisonings using all agrochemicals including insecticides was 604, with 395 deaths, in a population

of 12.6 million and with 1749 total recorded suicides. Two things need to be said about these figures. Firstly, they are obviously incomplete as many suicides are not investigated nor even reported in Malaysia, particularly in rural areas. The problem is thus most likely to be larger than reported. Secondly, there appears to be some confusion between accidents and suicides, both categories being reported together as suicides. Paraquat poisoning in Eire has been extensively reviewed by Fitzgerald^{2,16}. The general religious ethos of the country, however, almost certainly has led to reporting errors and it is not easy to set Fitzgerald's 136 cases into a context of all deaths from poisoning, nor of suicides generally. It is likely, however, that in terms of total cases per unit of population the Irish Republic has the greatest problem; as Fitzgerald remarks¹⁶, it is 'an unenviable record'.

3.2 APPROACHES TO THERAPY

A consideration of the pharmacokinetics of paraquat, as discussed in Section 1, with especial reference to the rapid peaking of plasma levels after ingestion, underlines the necessity of therapeutic measures to be introduced at the earliest possible moment in all cases of significant poisoning if there is to be any chance that treatment will be effective. As with all cases of poisoning, irrespective of the agent, treatment may be directed towards,

- (a) the prevention of significant absorption of the material from the gut by rapid removal/elimination or neutralisation,
- (b) the rapid removal of absorbed material from the circulation and,
- (c) the introduction of specific therapeutic measures designed to inhibit or block the action of the poison in the body or neutralise its toxic affect on body processes.

All three of these approaches have been tried in cases of paraquat poisoning with very varying degrees of success. Before going on to discuss the various forms of treatment that have been advocated it is necessary to consider briefly the indications for starting active treatment in cases of paraquat poisoning.

3.2.1 INDICATIONS FOR ACTIVE TREATMENT

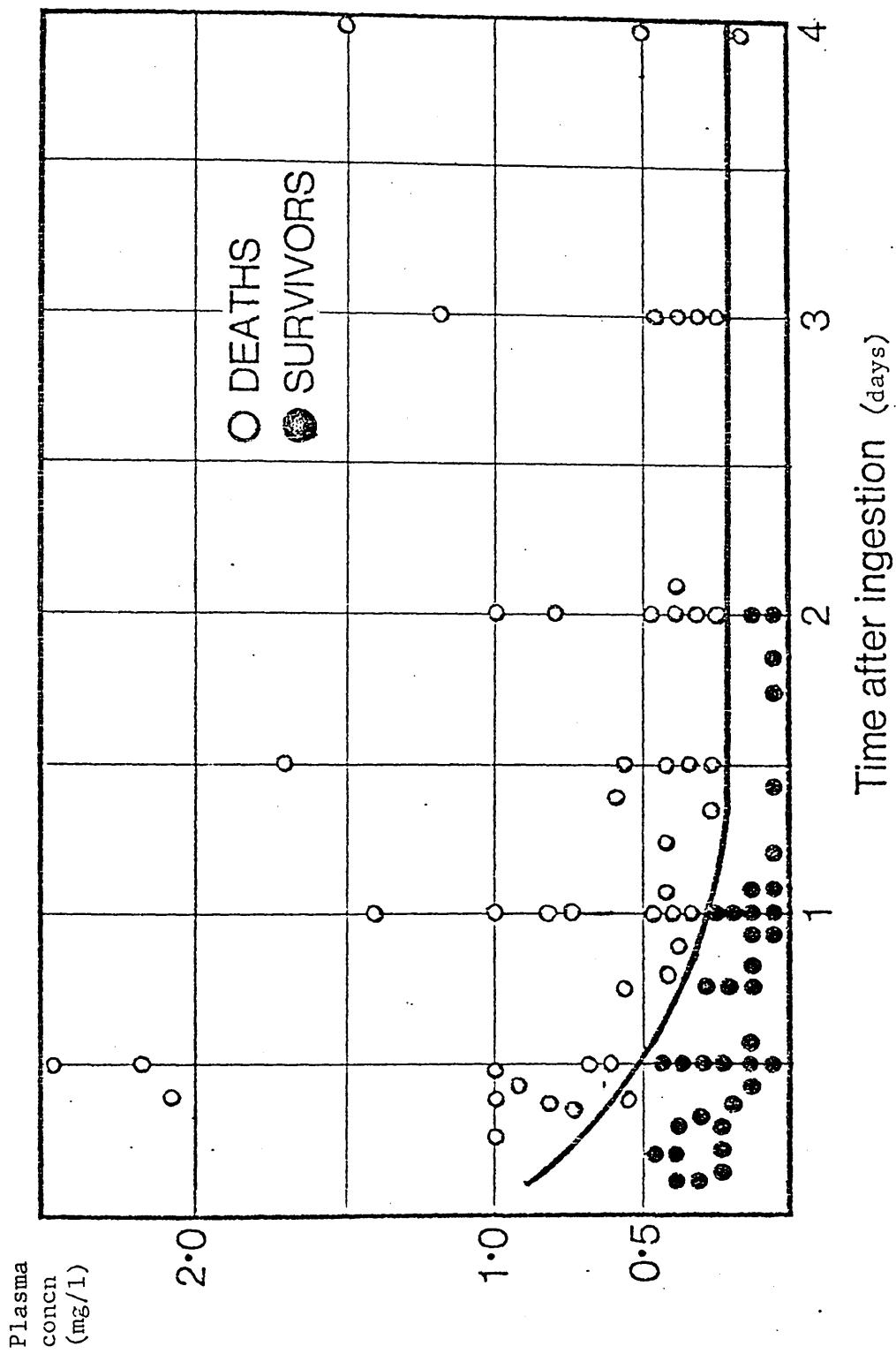
The onset of serious symptoms may be delayed in cases of paraquat poisoning. Clinical symptoms are therefore not a good indication of the severity of poisoning. Treatment should be based in the first instance on the history provided by the patient or by a relative or friend. This should be coupled with the simple qualitative test that may be applied to the urine to determine whether or not paraquat is being excreted. As a stomach wash-out should also be performed as a routine emergency measure in all cases of suspected paraquat poisoning, the same qualitative test may be applied to the stomach contents (or vomitus). It must be emphasized, however, that while such qualitative tests will confirm whether or not paraquat has been ingested, they are of little value in prognosis and may, at times, give misleading results. It has been suggested⁵ that an urinary excretion of paraquat of more than 1 mg per hour after eight hours have elapsed from ingestion is indicative of a poor prognosis. It should be noted, however, that if therapy is to be effective, it is essential that it is begun long before eight hours after ingestion.

The value of the history from the patient is related principally to two matters: the time at which the paraquat was ingested and the approximate amount taken. In those cases in which one of the granular formulations has been used, it is usually possible to obtain an accurate estimate of the amount ingested, but in cases in which the liquid concentrates have been used, this is often more difficult to determine and it may only be possible to make an approximate estimate of the quantity taken. The importance of these factors will be discussed later.

The history, taken in conjunction with the qualitative tests of urine or gastric contents for paraquat, may be used as indications to start treatment and a good history is likely to provide some guidance on the likely outcome and effectiveness of that treatment. Further objective guidance may be obtained from the results of plasma paraquat estimations. Relatively simple colorimetric¹⁷ or the more recently introduced radioimmunoassay methods¹⁸ may be used to provide rapid estimations of the plasma paraquat concentration. Proudfoot and his colleagues¹⁹, in a two centre survey have been able to demonstrate the prognostic value of such measurements, showing that there is a good prognosis in those patients whose plasma paraquat concentrations do not exceed 2.0, 0.6, 0.3, 0.16 and 0.1 mg per litre at 4, 6, 10, 16 and 24 hours respectively after ingestion. This conclusion is borne out by hitherto unpublished data from cases for whom plasma paraquat estimations were performed at ICI Ltd, Central Toxicology Laboratory (fig 3.1).

The patient's history taken in conjunction with the plasma paraquat concentration determined on blood taken at the time of hospital admission, will provide a rational basis for the physician to decide whether treatment should be vigorously pursued or whether it should be merely palliative.

FIG. 3.1: PLASMA PARAQUAT CONCENTRATIONS RELATED TO TIME FROM INGESTION



3.2.2 TREATMENT METHODS

THE PREVENTION OF ABSORPTION

The first approach in the prevention of absorption of any ingested material is its removal from the stomach. Because of the rapidity of absorption, evidenced by early peak plasma paraquat levels, it is essential that vomiting should be induced as a first aid measure (one of the few occasions when the induction of vomiting should be recommended). The further aspiration of stomach contents or gastric lavage should be undertaken as soon as the patient arrives at hospital. By themselves, such measures are unlikely to be life saving and fatalities have followed effective gastric lavage even when performed within one hour of ingestion²⁰⁻²². Moreover, since the undiluted commercial formulations of paraquat are highly irritant and corrosive, great care is necessary in the passing of stomach tubes to prevent perforation of the oesophagus or stomach¹⁰.

The work of Smith and his colleagues²³, following on the studies of Clark²⁴, has provided a rational basis for the use of clay-based absorbent materials in order to bind the paraquat lying in the gut and prevent any further absorption into the body. Their work demonstrated that the administration of Fuller's Earth to paraquat-dosed rats dramatically increased their survival and it was suggested that the use of this material should form the basis of the treatment of human poisoning.

A variety of other adsorbent materials have been evaluated²⁵, but the naturally occurring aluminium silicate-based minerals (Fuller's Earth, bentonite, etc) are undoubtedly the most efficient, which accords with what is known of the inactivation of paraquat by the soil²⁶ (see also Section 1.2). There are differences, however, in the adsorbent qualities of these minerals and Fuller's Earth is the most efficient binder of paraquat. Table 3.5 sets out the differences in adsorbing capacity between Fuller's Earth (Surrey finest grade) and another naturally occurring aluminium silicate used for therapeutic purposes ('Adsorbin', Sankyo Ltd). This latter material will be seen to have about 70 per cent of the capacity of Fuller's Earth, weight for weight. The adsorbent should be administered as a 10 per cent suspension, the volume required will be discussed later.

The administration of the adsorbent material should be associated with vigorous purgation in order to flush the gut as quickly as possible. Mannitol solution (20%) is probably the best purgative available and a satisfactory faecuresis will usually be obtained with doses in the range of 200 to 400 ml, although this may need to be repeated for several doses. The dose required, in fact, is simply that necessary to produce rapid and as near complete as possible purging of the gut, which should be continued until there is evidence of the adsorbent material being passed in the faeces. This should be achieved as rapidly as possible, certainly within four hours of instituting therapy²⁷.

TABLE 3.5 ADSORPTION CAPACITIES FOR PARAQUAT OF
TWO NATURALLY OCCURRING ALUMINIUM SILICATES

	Mg paraquat adsorbed/g dry weight clay	
	Maximum adsorption capacity	Tightly bound capacity
Fuller's Earth (Surrey finest)	63	30
Adsorbin (Sankyo Ltd)	50	20

Data from Prashad S, 1979 (personal communication)

Two considerations will affect the success of this form of therapy. The first is the volume of adsorbent material administered. If a dose of 5 g of paraquat ion has been ingested (equivalent to only 25 ml of 'Gramoxone') then, on the basis of the data in table 3.5, something in the order of 100 g of adsorbent clay will be required to bind this paraquat in the gut, that is 1 litre of a 10 per cent suspension. In cases in which commercial concentrates have been used the amount ingested will frequently be in excess of 5 g paraquat ion, thus requiring the administration of very large volumes of Fuller's Earth suspension over a very short time span.

It seems highly probable that in the past there has been serious undertreatment of paraquat poisoning, both in respect of the amount of adsorbent material administered and the period of time over which it has been given. There seems little doubt that the earlier use of the rat as a model for human poisoning seriously misled many workers and it was too readily assumed that paraquat absorption was relatively slow allowing a long time span for the administration of adsorbents. The early editions of the ICI Ltd Treatment Booklet issued to hospitals and treating physicians in the United Kingdom and elsewhere, for example, suggested that Fuller's Earth could be effectively administered for as long as 48 hours after paraquat ingestion. Such treatment regimes are no longer tenable and, in the light of present knowledge, should be considered virtual malpractice.

The clinical problems associated with the administration of such large volumes of fluid over such a short time period are considerable. Such suspensions are highly unpalatable and it is not uncommon for patients to be unable to swallow these large quantities of unpleasant fluid, particularly if there is associated oral or bucco-pharyngeal ulceration. Higher concentration suspensions (up to 30 per cent) were previously advocated, but these are more unpalatable than the weaker suspensions, more difficult to swallow and, in addition, there is the likelihood of the material impacting at the pylorus.

The use of gastric or duodenal intubation may help to overcome this problem, but, although not widely used in the United Kingdom, the best means of both administering adsorbent and clearing the gut is by the use of gut lavage as advocated by Okonek and his co-workers^{28, 29}. The technique involves the rapid passage of a large volume of fluid (14 to 18 litres) through the gut at a rate of about 75 ml per minute using a stomach tube and peristaltic pump. The irrigation fluid is normally a physiological solution such as Ringer's solution and 250 to 500 ml of a 10 per cent suspension of an adsorbent clay is fed into the gut each hour through a by-pass. The whole procedure is completed in less than 4 hours. Such therapy is not without its complications, however. Perforation of the gut wall may occur (particularly oesophagus or stomach) and fluid and electrolyte balance may be seriously disturbed and will require careful maintenance and continuous monitoring.

The second limiting factor that will reduce the effectiveness of adsorbent/purgative therapy has already been alluded to briefly, namely the speed at which paraquat is absorbed from the gut into the circulation. Recent animal work (discussed in Section 1.2) together with observations such as those of Proudfoot¹⁸, indicate that most absorption will have taken place within four hours from ingestion. Unless vigorous therapy can be instituted within this time, it is unlikely to be effective in those patients who have taken potentially lethal amounts. The importance of the time factor in treatment will be demonstrated later in the discussion of the author's series of cases. Delayed treatment together with under-treating may be responsible for the failure of Fitzgerald and his colleagues³⁰ to demonstrate any improvement in survival after paraquat poisoning when comparing mortality before and after the introduction of the Fuller's Earth regime in an extensive survey of Irish experience.

THE REMOVAL OF PARAQUAT FROM THE CIRCULATION

Paraquat does not bind to plasma macromolecules (Rose M S, 1976, unpublished data) and may thus be removed readily from the circulation by both haemodialysis and haemoperfusion. The latter, using charcoal columns, is much the more efficient and effective down to very low plasma concentrations of paraquat^{28, 29, 31-39}. Clearance values of approximately 90 ml/minute may be obtained with some columns at plasma concentrations in the range of 1.0 to 20.0 mg/litre. At plasma concentrations below 1.0 mg/litre,

although the efficiency is markedly reduced, it is still effective (Widdop B, 1978, personal communication).

It is important to distinguish clearly between two very distinct possible indications for the use of haemoperfusion or haemodialysis. These measures may be used to remove paraquat from the circulation or they may be used to support the kidney through a period of transient or incipient failure resulting from the toxic effect of paraquat. Both the indications and the likely effectiveness in these separate situations are very different, but this is not always made clear in the numerous literature references. Kidney support in renal failure is of great clinical value, but although there is no doubt about the effectiveness of haemoperfusion in removing paraquat from the circulation, there is more doubt about its real therapeutic value when used for this purpose.

The most important factor limiting the therapeutic effectiveness of these measures as a treatment for paraquat poisoning is, once again, that of time from ingestion. Haemoperfusion is only indicated in those situations where the plasma paraquat levels are approaching or exceeding the critical concentrations at given times¹⁸. In the great majority of cases in which such treatment would be of value, the peak plasma levels and the bulk of absorption has taken place before haemoperfusion could be started. By that time the target organs will have already received a substantial (and possibly lethal) dose of paraquat and the reduction of circulating levels will have little effect in preventing the vicious cycle of pathological change.

Even when it has been possible to set up haemoperfusion within three hours of poisoning, it has not prevented fatalities^{28,31,32,39} and, as will be discussed later, these measures failed to show any clear evidence of benefit in the author's series. However, note should be taken of the two cases reported by Okonek and his colleagues^{37,38} in which plasma paraquat levels were greatly in excess of the critical values indicated by Proudfoot¹⁸ or reported here (fig 3.1). The presumed dose was in the order of 15 to 20 g paraquat ion (3 to 4 mouthfulls of 'Gramoxone'), a dose at which there have been no survivors in the author's series, previously reported⁴ or discussed later, nor in the extensive survey of Fitzgerald². Haemoperfusion was maintained for two to three weeks for 8 hours per day suggesting that if it is begun early enough and pursued with vigour, it may be possible to remove paraquat from the circulation at a rate faster than the lung is able to accumulate it. Further clinical experience is required before Okonek's claims for haemoperfusion can be generally substantiated. The fact that it is now possible to make quite accurate predictions of the likely outcome of poisoning on the basis of plasma paraquat estimations makes the evaluation of the actual effectiveness of such newer methods of treatment a real possibility.

Forced diuresis has been advocated by some workers⁴⁰⁻⁴², but it has no real place in the treatment of paraquat poisoning.

As noted earlier (Section 1.2) paraquat is excreted by glomerular filtration coupled with active tubular transport. Neither of these excretion mechanisms is affected by forced diuresis and in consequence the use of this procedure will not increase the renal

excretion of paraquat. Further, it is a potentially highly dangerous technique, particularly in paraquat poisoning in which there is likely to be early renal damage. Even if this is transient, the administration of large volumes of fluid with diuretics is likely to be an embarrassment to the kidney and will lead to the patient becoming rapidly waterlogged. Such a situation will dramatically, even fatally, increase the pulmonary oedema.

THE USE OF 'ANTI-PARAQUAT' THERAPY

There have been a number of approaches to the treatment of paraquat poisoning which have been designed either to prevent or to reverse the effects of paraquat on the end organs. Some of the more important of these will be discussed briefly.

(a) Superoxide dismutase (SOD) and d-propranolol

The endogenous enzyme SOD, which dismutates the superoxide radical to form hydrogen peroxide (see Section 1.2.3), prevents the formation of other free radical species (especially the hydroxyl radical). The fact that the superoxide radical is produced as a result of the cyclic reduction and oxidation of paraquat in the cell has led a number of workers to advocate the use of SOD to 'mop up', the excess superoxide ions. The measure was given some support from the in vitro effectiveness of SOD in rat liver microsomal systems⁴³. To this was linked the use of β -adrenergic blocking agents such as d-propranolol which were thought to displace either or inhibit the uptake of paraquat by the lung as demonstrated by in-vitro studies⁴⁴. Although some success was claimed

by a number of workers for this approach to treatment⁴⁵⁻⁴⁹, these claims have not been borne out by further experience, either experimental or clinical⁵⁰⁻⁵². Further, considerations of the biochemical mechanisms in paraquat poisoning (see Section 1.2) make it unlikely that the application of exogenous materials would affect sub-cellular events. This form of therapy was not used in any of the 108 cases collected by the author and to be discussed later.

(b) Anti-inflammatory agents and immunosuppressants

The use of anti-inflammatory agents, particularly steroids and a variety of immunosuppressants, such as bleomycin, azathioprine or cyclophosphamide, have been used separately or in various combinations in the treatment of paraquat poisoning^{32,47,53-56}. The approach is purely empirical. Because there is an inflammatory component in the toxic response and because fibrosis is the dominant pulmonary effect, these agents were used in an attempt to reduce inflammation and reverse the fibroblastic response. While there may be some palliative value in the use of steroids, these agents have no effect on the development of the toxic tissue damage and the ultimate fibrosis.

It has been argued that steroids have a place in those cases in which there has been severe adreno-cortical damage⁵⁷. The use of steroids in such cases, however, while of value

in reversing the effects of adrenal shock, is unlikely to prove of lasting effect since doses sufficiently high to cause adrenal insufficiency will be invariably fatal.

(c) Hypoxic regimes and PEEP ventilation

The enhancement of paraquat toxicity by high ambient oxygen tension is a direct corollary of the consideration of the theoretical aspects of paraquat poisoning and has been demonstrated in animal experiments ⁵⁸⁻⁶¹. For this reason it is important to withhold the administration of oxygen to those suffering from paraquat poisoning until as late a stage as possible. On the other hand, the administration of hypoxic breathing mixtures is of very limited value in cases of human poisoning ^{32,50}, and has not protected the lung against the toxicity of paraquat in experimental animals ^{62,63}, in spite of some early claims to this effect ⁶⁴.

A variant approach to low oxygen therapy has been pursued by Douze and his co-workers in Holland ⁶⁵⁻⁶⁷. The principle of the method is to reduce arterial oxygen tension to between 50 and 70 mm of mercury by the administration of nitrogen, together with positive end-expiratory pressure ventilation (PEEP). The patient is sedated with the use of diazepam and muscular paralysis is achieved with tubocurarine. At the same time as artificial ventilation is applied, there is a programme of vigorous haemoperfusion. It is very difficult, however, to

judge the real effectiveness of this form of therapy.

It is certain that treating physicians would agree that the use of PEEP is valuable in the terminal care of paraquat poisoning, allowing easier nursing and preventing the gross dyspnoea which is distressing to patients, relatives and staff (Vale J A, 1978, personal communication). Claims for the success of this form of treatment in paraquat poisoning are much less certain. In theory PEEP ventilation should help to prevent atelectasis and reduce pulmonary oedema, but clinical evidence for this is sadly wanting and the relatively small reduction of arterial oxygen tension would have no effect on tissue concentrations. As an active therapy, PEEP ventilation with low oxygen therapy has not been satisfactorily demonstrated to have any significant effect on the course of poisoning. On the other hand, PEEP ventilation certainly has a place in general supportive therapy.

One point should be added: although low oxygen therapy has not been shown to have any clinical benefit, it is well established that the administration of oxygen at concentrations greater than ambient is contraindicated, except as a last resort in terminal cases. In all cases of paraquat poisoning, the use of oxygen should be delayed for as long as possible.

3.3 THE EFFECTIVENESS OF THERAPY

There have been a large number of reports of recovery after paraquat poisoning, sometimes claimed to be as a result of the use of one or another form of therapy. Some reports frequently fail to provide details of the dose of paraquat ingested, or the length of time that had elapsed before therapy was started. Any investigation of the effectiveness of therapy must take both these basic considerations into account. The obvious measure of success is the number of patients surviving after a potentially lethal dose, but an additional measure is the length of survival time in fatal cases indicating whether treatment increased the period of survival in fatal cases. Both these indicators of effective therapy will be examined in turn.

3.3.1 LENGTH OF SURVIVAL IN FATAL POISONING

The effectiveness of therapy will be shown primarily in improvements of overall survival rates, but the length of survival after ingestion of fatal doses will also give some indication of whether newer forms of therapy are having an effect on the clinical course. In order to determine whether there was any objective evidence for a change in survival time as the result of changes in treatment, it was decided to examine the data existing in the 'Incident File' of ICI Ltd from 1970 to the end of 1978. The records are not complete, but numbers are sufficient for comparative purposes. The use of Fuller's Earth with purgatives, together with haemodialysis and haemoperfusion became generally established in treatment from the beginning of 1975. The cases were therefore divided into those occurring up to December 1974 and those occurring

thereafter. Only those cases for which there was a reasonable estimate of dosage were used in the comparison and it was also decided to omit those cases in which dosage was sufficiently high that the outcome of poisoning was unlikely to have been affected by therapy (on the basis of published evidence⁵², this was set at 10g paraquat ion). A large number of cases in the files were excluded on this criterion as doses were too high or not recorded. It must be recognised, also, that in most cases of poisoning with liquid concentrates, the estimates of dosage are likely to be no more than approximations..

The results of this comparative study are set out in table 3.5. It is apparent that there is a very marked difference between the mean survival times in the two group, although mean doses are very comparable. A Student's 't' test applied to the two sets of survival times indicates a difference between them of such high mathematical significance that some factor or factors appear to be operating in one group and not the other ($t = 3.1$; $df = 42$; $P < 0.0025$).

While it may reasonably be concluded from this data that the introduction of newer treatment methods has done nothing to increase the survival time in fatal cases, it is not so easy to account for the highly significant reduction in survival time from a mean of nearly 11 days to less than half that time at equivalent dose levels. It could be that over-heroic therapy has hastened the patient's death in the past by some upset in electrolyte and fluid balance. Further, it is known that a number of cases certainly have occurred in which there has been fatal perforation of a friable oesophagus by a stomach tube and in which there has been fatal inhalation of Fuller's Earth. It is difficult however to

TABLE 3.5. COMPARISON OF SURVIVAL TIMES IN FATAL
CASES OF PARAQUAT POISONING AT INGESTED
DOSES BELOW 10g PARAQUAT ION, BEFORE
AND AFTER DECEMBER 1974

Period	No. of Cases	Mean dose (g) (below 10g)		Mean Survival time (days)	
		Mean	SD	Mean	SD
Jan 1970 - Dec 1974	17	6.0	3.0	10.7	10.8
Jan 1975 - Dec 1978	27	6.7	3.3	3.8	3.4

(Differences between survival time are highly
significant : $t = 3.1$; $df = 42$; $P < 0.0025$)

to account for such a marked reduction in survival time by iatrogenic causes alone.

It is possible, however, that with the increasing recognition that intensive supporting therapy is of little value in those cases where a downhill course is apparent, there has been less willingness to submit patients to heroic measures which, while maintaining life for a period, have no influence on the eventual outcome and could very well be uncomfortable or even distressing to the patient. The reduction in survival time may thus reflect a reduction in the use of life support systems in recognisably fatal cases, but this is no more than a surmise. What may be said, however, is that the available evidence indicates that newer treatment methods have not increased this period of survival from ingestion to death in fatal cases.

3.3 RECOVERY RELATED TO THE TIME TREATMENT WAS INSTITUTED,
TREATMENT METHOD AND INGESTED DOSE

A total of 108 cases were followed-up by the author in the period 1976-1979 as a result of the co-operation of treating physicians. The data collected included the age, sex and as far as possible the occupations of the patients, together with details of therapy, clinical and laboratory measurements and the eventual outcome. The time that had lapsed between ingestion and the institution of therapy was noted in all but twelve of the cases. Urine and plasma levels of paraquat were recorded where these were available. The actual number of deliberate paraquat poisonings was greater than the 108 reviewed, but for the purpose of this study it was decided to include only those cases in which there was a clear

statement of the amount ingested. Cases in which the statement of dosage was in such terms as 'a mouthful' were rejected as not being sufficiently precise.

The approach to treatment in all cases reviewed comprised the standard recommended treatment: the initial induction of vomiting and/or gastric lavage, followed by the oral administration of repeated doses of Fuller's Earth suspension and saline purgatives or mannitol. Additional therapeutic measures included the use of forced diuresis, haemodialysis and haemoperfusion, together with corticosteroids and immunosuppressive agents.

RESULT AND DISCUSSION

The age and sex distribution of the 108 cases is shown in Figure 3.2. There were 84 males (77.8%) and 24 females (22.2%). The age distribution in both sexes is skewed, but two peaks appear among the males (between 20 and 30 years and 50 and 60 years of age) whereas only a single peak occurs in the case of females (between 30 and 40 years of age).

As will be seen from the figures, these two age groups in males (ie from 20 to 30 and 50 to 59 years of age) account for 50% of all the male paraquat poisoning cases. The reasons for these age peaks is not clear although unemployment may have been a factor in some suicides. Similarly, the female peak between 30 and 39 years of age accounts for approximately 30% of cases and over 50% fell in the age group 30-49 years. Menopausal depression may have been a factor in some of these cases. Virtually half the episodes (46.7%) occurred in the summer months

FIG 3.2: AGE AND SEX DISTRIBUTION OF PARAQUAT POISONING

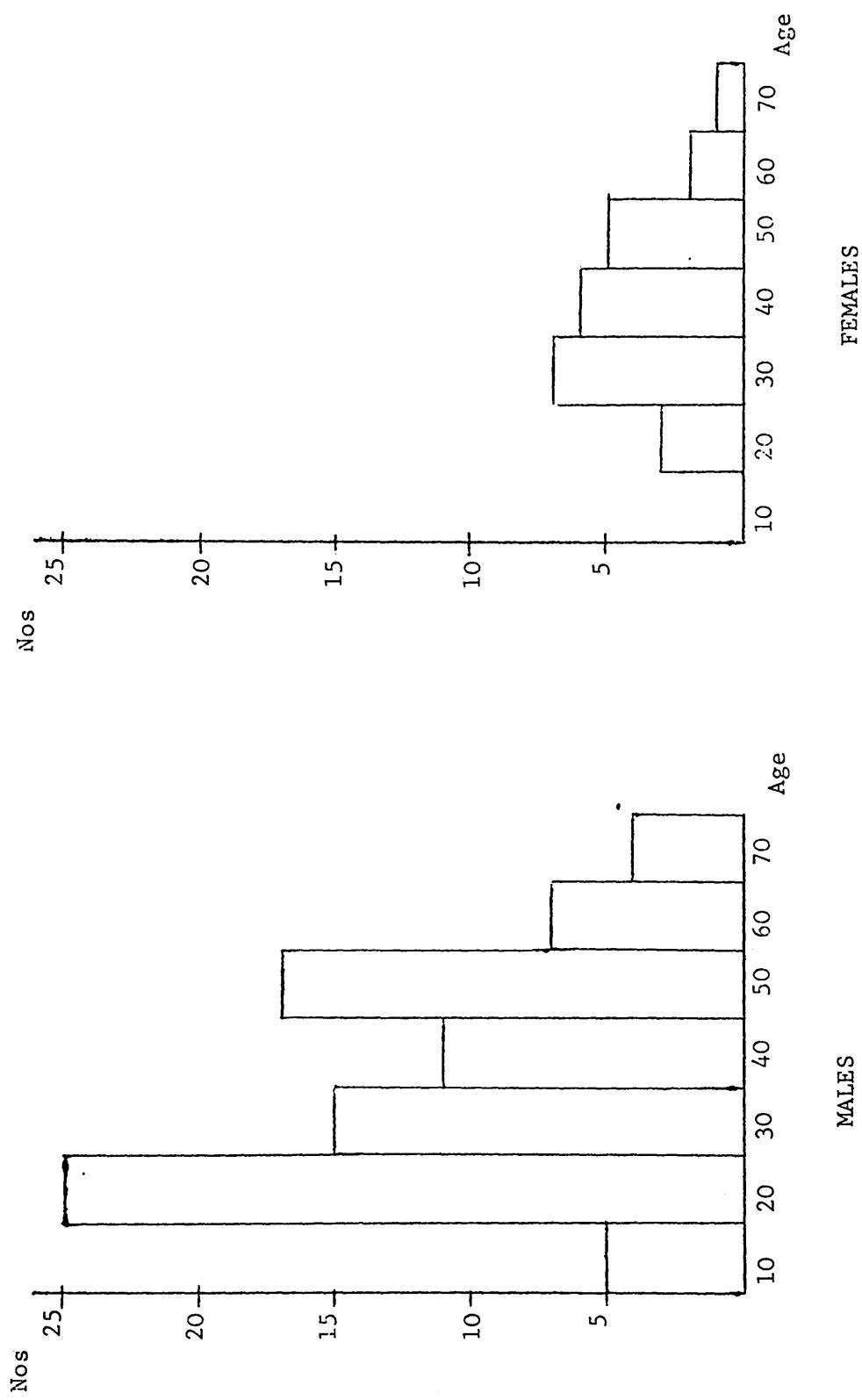
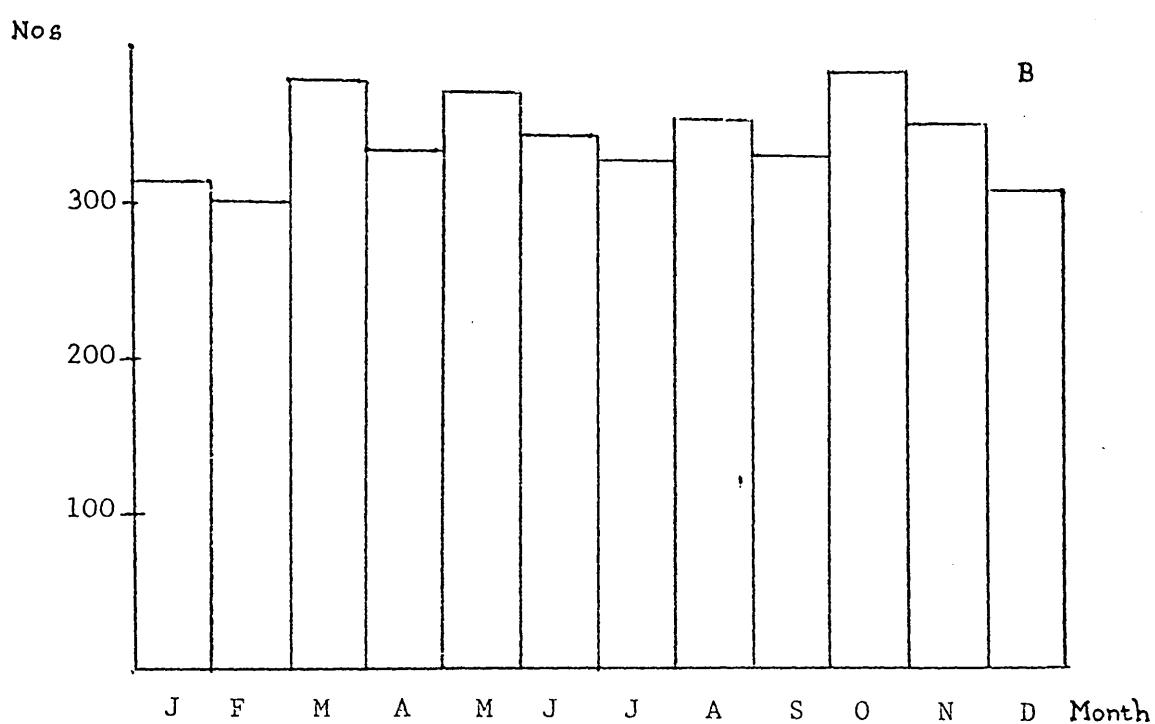
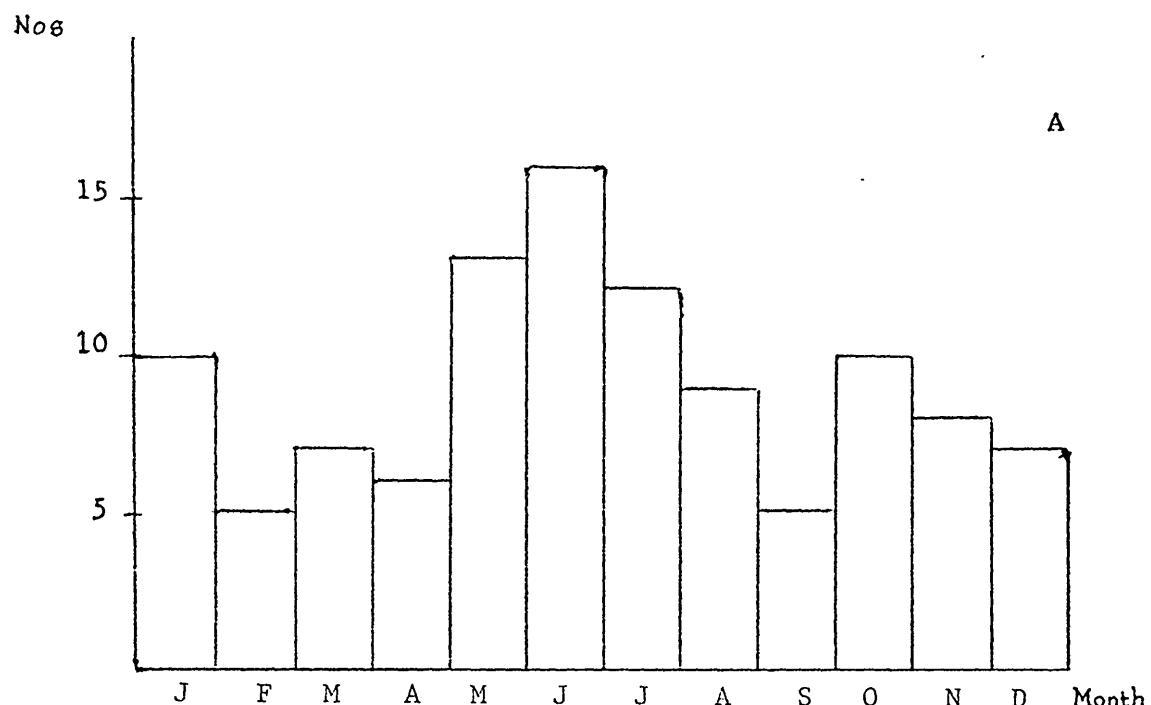


FIG 3.3: SEASON INCIDENCE OF PARAQUAT SELF POISONING (A)
COMPARED WITH SEASONAL INCIDENCE OF ALL SUICIDES (B)



May to August with a peak in June, which corresponds very largely to the period of the year when paraquat would be in use as a herbicide in domestic situations (fig. 3.3), thus differing from the relatively even distribution of self-poisoning throughout the year as a whole in the UK.

It was not possible to elicit psychiatric histories from all the cases, but table 3.6 provides evidence that previous mental illness is a significant factor in such poisoning cases. In most cases this had been severe endogenous depression. Alcoholism was a feature of only four cases. Ten patients had histories of previous attempts at suicide. Three cases were known to have been suicidal gestures following domestic rows, sadly two of these were fatal.

The social background of the patients reviewed was not easy to elicit, especially in females who were described mainly in case notes as housewives. However, job classification suggested that at least half of the male cases came from social classes IV and V (unskilled workers) and very few from the professional and skilled social groups.

Where possible, the source of paraquat was noted in cases where agricultural concentrates were used for self-poisoning. The results are shown in table 3.7. Approximately half the cases had no entitlement to access to agricultural concentrates such as 'Gramoxone'. In one case a young man admitted to stealing the material from a nearby farm. Another 12 cases obtained the concentrates from relatives and friends, decanted into other containers. In each case it was the farmers who were prepared

TABLE 3.6 PSYCHIATRIC BACKGROUND TO PARAQUAT
POISONING CASES

	Males		Females		Total	
	No.	%	No.	%	No.	%
Previous history of mental illness	18	21.4	9	37.5	27	25.0
Previous history of personality disorder	1	1.2	0	-	1	0.9
History of alcoholism	3	3.6	1	4.2	4	3.7
History of previous suicidal attempts	9	10.7	1	4.2	10	9.3
No previous history of mental illness obtained	3	3.6	0	-	3	2.8
Not known	50	59.5	13	54.1	63	58.3
Total	84	100.0	24	100.0	108	100.0

TABLE 3.7 : SOURCE OF PARAQUAT IN SELF-POISONINGS USING AGRICULTURAL CONCENTRATES

	Numbers		%
	Male	Female	
Entitled to possess concentrate, or easy access through work	17	1	36
Obtained through relatives, friends etc. Stored in unauthorised containers	10	2	24
Bought openly from merchants, stores etc, by unauthorised purchasers	8	3	22
Stolen (admitted)	1	-	2
Source not known	6	2	16
	42	8	100

to undertake such a dangerous and illicit practice who are most to blame. In addition, a further 11 cases, according to their own stories, bought 'Gramoxone' openly 'across the counter' from agricultural merchants or similar stores with apparently no questions asked and no signing of the poisons register. The occupations of these purchasers ranged from ordinary housewives to a mechanic, bus driver and a builder, none being even remotely concerned with agriculture. Such apparent ease in obtaining highly toxic material in an illicit fashion must give cause for concern.

The overall mortality in the series was 50.0 per cent (54 deaths in 108 cases). Mortality was much higher in cases of poisoning with liquid concentrate formulations (mainly 'Gramoxone') where there were 42 deaths from 50 cases (a mortality of 84.0%), but there were only 12 deaths from 58 cases of poisoning with the retail granular formations (20.7%) (tables 3.8 and 3.9). These differences are largely a reflection of the size of dose ingested: larger quantities of paraquat are usually taken when liquid formulations are used. This cannot be the whole story, however, as a comparison of mortality at equivalent doses (table 3.10) indicates a higher mortality following the ingestion of liquid concentrates than from the retail formulations. It is possible that this variation may be due to the differences in concentration in the ingested material. The concentrates are normally ingested neat, at a concentration of 20% paraquat ion, but the granular material must first be dissolved in water. The stories obtained from patients would suggest that the concentration of this material is usually well below 10 per cent. The differences in the

TABLE 3.8 DEATHS FROM PARAQUAT POISONING

Formulation	No. of Deaths	No. at Risk	Mortality %
Concentrates (liquid)	42	50	84.0
Granular (solid)	12	58	20.7
Totals	54	108	50.0

TABLE 3.9 OUTCOME OF PARAQUAT POISONING RELATED
TO FORMULATION INGESTED

	Deaths		Recoveries		Total
	No.	%	No.	%	
LIQUID					
Gramoxone	38	84.4	7	15.6	45
Gramonol	2	66.7	1	33.3	3
Dextrone	2	100.0	0	-	2
GRANULAR					
Weedol	11	21.6	40	78.4	51
Pathclear	1	14.3	6	85.7	7
TOTALS	54		54		108

TABLE 3.10 COMPARISON OF MORTALITY FROM PARAQUAT
POISONING WITH DIFFERING FORMULATIONS
AT EQUIVALENT DOSES (2-10g PARAQUAT ION)

Formulation	No. of Cases	Deaths	Mortality %
Liquid concentrates	19	15	78.9
Granular	13	6	46.2
TOTAL	32	21	65.6

formulations (stabilizers, wetters, etc.) may also play a part in accounting for the differing mortality rates.

The relationship between the dose of paraquat ingested (in grams of paraquat ion), the time elapsed between ingestion and the institution of treatment and the ultimate outcome is shown in table 3.11. There were no survivors in this series among the 23 who had ingested more than 10 gm of paraquat ion (equivalent to 50 ml 'Gramoxone' or 6-7 sachets of 'Weedol') irrespective of the time at which treatment was instituted, and there was only one survivor from 16 cases who had ingested more than 5.0g of paraquat ion (equivalent to 25 ml 'Gramoxone' or 3-4 sachets of 'Weedol') but less than 10g. Such a dose of 'Gramoxone' represents no more than a single mouthful. Taking both these higher dose groups together, there were 39 patients of whom 13 were given proper treatment within two hours of ingesting paraquat and in only 8 cases was the institution of therapy delayed beyond 10 hours from ingestion. Nonetheless, there was only one survivor out of these 39 cases, suggesting strongly that doses in the area of 5g represent the maximum treatable ingested amount, particularly if there is any delay in instituting treatment beyond 2 hours after ingestion. The importance of the time factor in treatment is shown in table 3.12 in relation to the 'treatable' dose range of 2 to 10g paraquat ion. This correlates closely with the data on plasma paraquat levels indicating the rapidity of absorption.

The pattern of major organ damage in this series is shown in table 3.13. These figures are based on clinical observations and investigations and not on post mortem findings. The two

TABLE 3.11 OUTCOME OF PARAQUAT POISONING RELATED TO THE INTERVAL

BETWEEN INGESTION & TREATMENT AT DIFFERENT DOSE

Time interval before treatment	up to 2.0g		over 2.0 to 5.0g		over 5.0 to 10.0g		over 10.0g	
	Recovery	Death	Recovery	Death	Recovery	Death	Recovery	Death
Less than 2 hours	6	2	5	0	1	4	0	8
From 2 to 5 hours	12	2	3	3	0	4	0	7
From 5 to 10 hours	5	1	1	1	0	4	0	3
Over 10 hours	13	0	1	2	0	3	0	5
* Totals	36	5	10	6	1	15	0	23
Mortality (%)	12.2		37.5		93.7		100.0	

* In 12 cases it was not possible to estimate either the time of treatment or the actual dosage ingested.

TABLE 3.12 INGESTION/TREATMENT INTERVAL AND
OUTCOME OF POISONING AT DOSES BETWEEN
2.0g AND 10.0g PARAQUAT ION

	No. of recoveries	No. of Deaths	Total Cases	Mortality %
Up to 2 hours	6	4	10	40.0
From 2 to 5 hours	3	7	10	70.0
Over 5 hours	2	10	12	83.3
Totals	11	21	32	65.6

TABLE 3.13 THE PATTERN OF MAJOR ORGAN DAMAGE
IN PARAQUAT POISONING

	Fatal	Non-Fatal
Kidneys	5	7
Kidneys + Lung	22	3
Lung	2	4
Liver + Lung	1	2
Liver + Kidneys	2	1
Kidneys + Lung + Liver	21	1
Liver	1	2
Totals	54	20

fatal cases in which lung damage only was seen, were both treated with forced diuresis, and it is more than probable that the fatal pulmonary oedema was a result of over-energetic treatment rather than the paraquat itself. Hepatic damage alone was seen in only three patients, and there were 3 cases in which lung effects were seen in association with hepatic damage. The normal pattern, however, was for lung damage to follow evidence of renal failure. Renal damage in many cases was severe, judged from biochemical indices. The relatively high numbers showing renal involvement following 'Weedol' ingestion may reflect the additive effect of the diquat also included in this formulation. Two of these cases showed marked central nervous system involvement with convulsions and another two cases showed methaemoglobinaemia, a phenomenon that is difficult to explain. It is worth noting that among the deaths there were two who died from the inhalation of Fuller's Earth, both of whom had taken less than 2g paraquat ion and three who apparently died from myocardial infarction during therapy, although this may have been a toxic myocarditis which has been observed in a number of cases (Vale, J A, 1978, personal communication). There was a further case who died with extensive intravascular clotting.

The introduction of Fuller's Earth as the basis of therapy, designed to prevent the initial absorption of paraquat from the gut, was widely welcomed with cautious optimism as a possible answer to a hitherto insoluble problem. However, as discussed

earlier (Section 3.2) the only large scale review of poisoning undertaken so far has failed to show any significant improvement in mortality following the introduction of Fuller's Earth³⁰. Fitzgerald's conclusion in that study was that the only patients likely to have benefited from therapy were those treated within six hours of ingestion and who had taken between 5 and 30 ml of 'Gramoxone' (equivalent to 1 to 6 gm of paraquat ion). The French review of poisoning with paraquat would lower the upper level of treatable dose to 4 gm paraquat ion⁶. The indications of the present study would put the upper limit of treatable ingested dose at just above 5g paraquat ion (table 3.11), in close agreement with the conclusion of Fitzgerald.

The mortality pattern in the present series of 108 cases is very similar to that of Fitzgerald's series. The overall mortality rate is similar and the great majority of survivors had taken less than 2 gm of paraquat ion, a dose level at which only minimal therapy is probably necessary. On the other hand, there were no survivors at doses above 10 gm paraquat ion, irrespective of the time at which therapy was instituted or the vigour with which it was applied. An important intermediate group is thus disclosed who have taken more than 2 gm, but less than 10 gm of paraquat ion and in whom treatment may be shown to be of value. The critical factor in this group, however, is the time at which treatment is started. Table 3.12 shows that the chances of survival are very much poorer if the start of

treatment is delayed beyond 5 hours, whereas there were 6 survivors out of 10 cases treated within 2 hours of ingestion in the same dose range. Time thus appears to be the critical factor and this is to be related to the rapid absorption of paraquat demonstrated by the early peaking of plasma paraquat levels (section 3.2.1 and fig 3.1). The practical success of therapy thus closely mirrors the picture obtained from considerations of absorption patterns. It is thus possible to set out the three minimum criteria for possible successful therapy:

1. an ingested dose less than 10 g paraquat ion
(equivalent to 50 ml 'Gramoxone'; 6 sachets of 'Weedol'). In reality, as already suggested, it is likely that the really 'treatable' dose is not more than 6 g paraquat ion, equivalent to 30 ml of 'Gramoxone' or 4 sachets of 'Weedol' (see table 3.11). The setting of too rigid a dose criterion could lead to the exclusion of cases that might benefit from early and vigorous treatment and, accordingly, an upper limit of 10g is suggested. This also allows for variations in the amount of paraquat available for absorption as a result of vomiting, existing stomach contents etc.
2. active therapy instituted within 5 hours of ingestion,
(ideally within 2 hours)
3. plasma paraquat levels below 2.0 mg/litre at 4 hours after ingestion or 0.6 mg/litre at 6 hours after ingestion.

The 'window' for introducing effective therapy is thus very small and while small treatable doses are the rule with the retail granular formulations ('Weedol' and 'Pathclear'), a single mouthful of the agricultural concentrate is potentially lethal.

The problem in assessing the value of treatment is to decide which aspect is the most important. Slightly more than half the patients in this series vomited spontaneously and frequently profusely, but this did not appear to influence the final outcome as there were as many who vomited among fatalities as survivors. However, there is a variety of factors such as time to vomiting and the volume distribution of paraquat in the stomach which would affect this situation. All patients received gastric lavage on admission to hospital followed by the administration of Fuller's Earth and purgatives. The importance of the time factor in treatment, related to what is known of gastric emptying, would suggest that gastric lavage is equally as important as the use of Fuller's Earth. This raises the whole question of the oral administration of this adsorbent. Two cases in this series died through the inhalation of orally administered Fuller's Earth. Furthermore, patients are generally intolerant of these suspensions especially when concentrated (eg 30%) and the problem is made worse in the presence of inflamed or ulcerated mouth and fauces with dysphagia or intractable vomiting. There is also some unpublished post-mortem evidence which suggests that the passage of Fuller's Earth across the pylorus into the duodenum is not as complete or as rapid as usually thought if the suspension is concentrated. For these reasons the regime of

Okonek and Hofmann^{28,29} using gut lavage with Fuller's Earth in saline is likely to be more effective in ensuring that the adsorbent reaches the small gut in sufficient quantities. However, unless this regime can be introduced rapidly it is not likely to be much more effective than present methods.

The use of a variety of adjuvant forms of therapy has been advocated, both to remove paraquat from circulation and to protect the lung. There was no evidence from this study that the use of such adjuvant therapy plays any part in increasing survival after poisoning. Table 3.14 indicates the apparent effectiveness of the most common forms of adjuvant therapy at various dose levels. It is not easy to separate the effects of individual forms of additional therapy, since all were combined with the basic form of treatment using Fuller's Earth and were also frequently used in combination together. It will be seen from the table that the mortality rates in the dose range 2.0 to 10.0g paraquat ion compare very closely with those shown in table 3.12, which sets out the overall mortality in this dose range. It would probably be argued by Okonek on the basis of his successful use of haemoperfusion^{36,38} that this regime was not pursued with sufficient vigour nor for a sufficient length of time to produce an effect in the cases in this series. The results following forced diuresis are markedly poorer, however, than those associated with other forms of therapy. This is likely to be related to the secondary effects of pulmonary oedema which, according to the case histories, developed in at least half the cases treated by this method. Such therapy is likely to be hazardous when the patient is developing oliguric renal failure.

TABLE 3.14 EFFECTIVENESS OF ADJUVANT THERAPY
IN PARAQUAT POISONING

Form of Therapy	Dose Range						Mortality % (2-10g range)	
	Less than 2g		Over 2g to 5g		Over 5g to 10g			
	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths		
Haemodialysis and/or haemoperfusion	9	1	5	2	7	6	9 9 66.7	
Forced diuresis	10	1	9	5	7	7	5 5 75.0	
Anti-inflammatory agents and/or immunosuppressants	1	0	4	1	8	7	9 9 66.7	

* Death from inhalation of Fuller's Earth

Furthermore, as noted earlier, it is a form of therapy contraindicated on theoretical grounds. None of the patients in this series received d-propranolol, nor was PEEP ventilation used. Neither form of therapy will prevent the progress of the lung lesion, although the latter is certainly of benefit in the terminal management of fatal cases.

Perhaps the most important aspect of this analysis of 108 cases of paraquat poisoning is the way in which it serves to emphasize both the very small dose range for which treatment is likely to be effective and the narrow time band available to institute such therapy once ingestion has taken place. The author's experience would suggest that neither of these issues is sufficiently understood, particularly in accident and emergency units to which the majority of patients are taken in the first place.

3.4 REFERENCES

- 1 PARK J, PROUDFOOT A T, PRESCOTT L F, Paraquat poisoning:
A clinical review of 31 cases. In: Clinical Aspects of Paraquat Poisoning. Fletcher K (ed). London, ICI Ltd 1975
46-54
- 2 FITZGERALD G R, BARNIVILLE G, FLANAGAN M, SILKE M, CARMODY M,
O'DWYER W F T, The changing pattern of paraquat poisoning:
An epidemiological study. J Irish Med Ass. 1978; 71 : 103-108
- 3 FITZGERALD G R, BARNIVILLE G, GIBNEY R T N, FITZGERALD M X,
Clinical, radiological and pulmonary function assessment in
13 long-term survivors of paraquat poisoning. Thorax 1979;
34 : 414-429
- 3a CARSON D J, CARSON E D, The increasing use of paraquat as a
suicidal agent. Forensic Sci 1976; 7 : 151-160
- 4 HOWARD J K, Recent experience with paraquat poisoning in
Great Britain: A review of 68 cases. Vet Human Toxicol 1979;
21 Suppl: 213-216
- 5 WRIGHT N, YEOMAN W B, HALE K A, Assessment of seventy cases
of paraquat poisoning. Brit Med J. 1978; 2 : 396
- 6 CONSO F, Intoxication aigüe par le paraquat. Bull Med Leg Toxicol 1978; 21 : 117-120
- 7 FLETCHER K, Paraquat poisoning. In: Forensic Toxicology.
Ballantyne B, (ed). Bristol, J Wright & Sons. 1974. 86-98

- 8 FRASER N C, Accidental poisoning deaths in British children:
1958-77. Brit Med J 1980; 280 : 1595-1598
- 9 HAVILL J H, ROTHWELL R P G, CHIN L, LENG R E, WARDILL J,
Accidental paraquat poisoning. N Z Med J 1977; 85 : 512-514
- 10 MALONE J D G, CARMODY M, KEOGH B, O'DWYER W F, Paraquat poisoning:
a review of nineteen cases. J Irish Med Ass 1971; 64 : 59-68
- 11 BINNIE G A C, Paraquat. Lancet 1975; i : 169
- 12 REBELLO G, MASON J K, Pulmonary histological appearances
in fatal paraquat poisoning. Histopathol 1978; 2 : 53-66
- 13 SCHLATTER I, Vergiftungen mit dem Unkraut vertilgungsmittel
Paraquat. Praxis 1976; 65 : 837-843
- 14 HEIJST A N P, VAN DOUZE J M C, PIKAAR S A. The National
Poison Information Centre. Ned Tijaschr Genersk 1976;
120 : 206-209
- 15 AMARASINGHAM R D, TI T H, A review of poisoning cases examined
by the department of chemistry, Malaysia, from 1968 to 1972.
Med J Malaysia 1976; 30 : 185-193
- 16 FITZGERALD G M, Paraquat poisoning. Irish Med J 1978;
71 : 326-377

- 17 CALDERBANK A, YUEN S H, An ion exchange method for determining paraquat residues in food crops. Analyst 1965; 90 : 99-106
- 18 LEVITT T, Determination of paraquat in clinical practice using radioimmunoassay. Proc Analyt Div Chem Soc 1979; Feb 72-76
- 19 PROUDFOOT A T, STEWART M S, LEVITT T, WIDDOP B, Paraquat poisoning; the significance of plasma paraquat concentrations. Lancet 1979, ii : 330-332
- 20 HENSEL G, DUERR F, Dialysis therapy in paraquat intoxication. Med Welt 1971; 45 : 1790-1794
- 21 NIENHAUS H, EHRENFIELD M, Pathogenesis of lung disease in paraquat poisoning. Beitr Pathol 1971; 142 : 244-267
- 22 TILLING W, Paraquat intoxication. Dtsch Med Wochenschr 1968; 93 : 2439-2441
- 23 SMITH L L, WRIGHT A, WYATT I, ROSE M S, Effective treatment of paraquat poisoning in rats and its relevance to the treatment of paraquat poisoning in man. Brit Med J. 1974; 4 : 596-571
- 24 CLARK D G, Inhibition of the absorption of paraquat from the gastro-intestinal tract by adsorbants. Brit J Indust Med 1971; 28 : 186-188
- 25 STAUFF D C, IRLE G K, FELENSTEIN W C, Screening of various adsorbants for protection against paraquat poisoning. Bull Environ Contam Toxicol 1973; 10 : 193-199

- 26 KNIGHT B A G, TOMLINSON T E, The interaction of paraquat with mineral soils. J Soil Sci 1967; 18 : 233-243
- 27 HOWARD J K, Paraquat poisoning: UK experience and its therapeutic implications. In: Proceedings of First Paraquat Clinical Meeting, Japan, Tokyo, ICI Ltd 1980, 37-42
- 28 OKONEK S, HOFMANN A, HENNINGSEN B, Efficacy of gut lavage, haemodialysis and haemoperfusion in the therapy of paraquat or diquat intoxication. Arch Toxicol 1976; 36 : 43-51
- 29 OKONEK S, HOFMANN A, Current aspects of the therapy of paraquat and diquat poisoning; gut lavage, haemodialysis and haemoperfusion. In: Clinical Aspects of Paraquat Poisoning, Fletcher K, ed, London ICI Ltd, 1977, 55-68
- 30 FITZGERALD G R, BARNIVILLE G, DICKSTEIN K, CARMODY M, O'DWYER W F, Experience with Fuller's Earth in paraquat poisoning. J Irish Med Ass 1979; 72 : 149-152
- 31 VALE J A, CROME P, VOLANS G N, WIDDOP B, GOULDING R, The treatment of paraquat poisoning using oral sorbents and charcoal haemoperfusion. Acta Pharmacol Toxicol 1977; 41 Suppl 11 : 109-117
- 32 SOLFRANK G, MATTHES G, CLARMANN M, BEYER K H, Haemoperfusion through activated charcoal in paraquat intoxication. Acta Pharmacol Toxicol 1977; 41 Suppl 11 : 91-101

- 33 WIDDOP B, MEDD R K, BRAITHWAITE R A, Charcoal haemoperfusion in the treatment of paraquat poisoning. Proc Europ Soc Toxicol 1977; 18 : 156-159
- 34 MAINI R, WINCHESTER J F, Removal of paraquat from the blood by haemoperfusion over sorbent materials. Brit Med J 1975; 2 : 281-282
- 35 OKONEK S, TONNIS H J, BALDAMUS C A, HOFMANN A, Haemoperfusion versus haemodialysis in the management of patients severely poisoned by organophosphorus insecticides and bipyridyl herbicides. Artificial Organs; 3 : 341
- 36 OKONEK S, BALDAMUS C A, HOFMANN A, SCHUSTER C J, BECHSTEIN P B, ZOLLER B, Two survivors of severe paraquat intoxication after continuous haemoperfusion Klin Wochenschr 1979; 57 : 957-959
- 37 BISMUTH C, CONSO F, WATTEL F, GOSSELIN B, LAMBERT H, Coated activated charcoal haemoperfusion: experience of the French anti-poison centres in 60 cases. Vet Human Toxicol 1979; 21 : 81-83
- 38 OKONEK S, BALDAMUS C A, HOFMANN A, Survival despite potentially fatal plasma paraquat concentrations. Lancet 1980, ii 589
- 39 YOSHIDA K, ASANO Y, et al, Effects of direct haemoperfusion on paraquat poisoning: a review of ten cases. J Japan Soc Nephrol 1980; 22 : 1001

- 40 KERR F, PATEL A R, SCOTT P D R, TOMSETT S L, Paraquat poisoning treated by forced diuresis. Brit Med J 1978; 3 : 290-291
- 41 FENNELLY J J, FITZGERALD M X, FITZGERALD O, Recovery from severe paraquat poisoning following forced diuresis and immunosuppressive therapy. J Irish Med Assoc 1971; 64 : 69-71
- 42 McGEOWN M G, Clinical aspects of paraquat poisoning
In: Clinical Aspects of Paraquat Poisoning. (ed. Fletcher K,) London, ICI Ltd 1977. 12-21
- 43 DAVIES D S, DAVIES D L, Effect of d-propranolol and superoxide dismutase on paraquat reduction and adrenochrome formation by rat liver microsomes. Fed Proc 1974; 33 : 228
- 44 MALING H M, SAUL W, WILLIAMS M A, BROWN E A B, GILLETTE J R, Propranolol treatment of experimental paraquat poisoning in rats. Fed Proc 1975; 34 : 226
- 45 AUTOR A P, Reduction of paraquat toxicity by Superoxide dismutase. Life Sci 1974; 14 : 1309-1319
- 46 DAVIES D S, CONNOLLY M E, Paraquat poisoning: possible therapeutic approach. In: Living Metabolism, Junod A F, ed London, Academic Press, 1975, 275-277
- 47 DAVIES D S, CONNOLLY M E, Paraquat poisoning: possible therapeutic approach. Proc Roy Soc Med 1975; 68 : 442

- 48 CONNOLLY M E, DAVIES D S, DRAFFEN G H, BENNETT P N,
DOLLERY C T, Clinical experience with paraquat poisoning.
In: Clinical Aspects of Paraquat Poisoning. Fletcher K, ed
London, ICI Ltd 1977. 1-11
- 49 PATTERSON C E, RHODES M L, Continuous intravenous superoxide
dismutase infusion in paraquat toxicity. Am Rev Resp Dis 1979;
119 (Suppl) : 346
- 50 FAIRSHTER R D, ROSEN S M, SMITH W R, GLASSER F L, MCRAE D M,
WILSON A F. Paraquat poisoning: new aspects of therapy
Quart J Med 1976; 45 : 551-565
- 51 SUZUKI H, TSUTSUI J, NAKAMURA Y, ITO Y, et al.
Studies on the toxicity of paraquat dichloride: 2,
The effectiveness of CDP-choline and superoxide dismutase
for treatment. J Japan Ass Rural Med 1976; 25 : 336-337
- 52 GIRI S N, HOLLINGER M A, SCHEIDT M J, The failure of
superoxide dismutase to modify paraquat-induced increased
pulmonary vascular permeability and oedema in mice.
An Rev Resp Dis 1979; 119 (Suppl) : 217
- 53 LAITHWAITE J A, Paraquat poisoning treated with immunosuppressants
and potassium aminobenzoate. Brit Med J 1979; 1 : 266-267
- 54 LAITHWAITE J A, Paraquat poisoning. Brit J Clin Pract
1975; 30 : 71-73

- 55 McCORMACK J, Paraquat poisoning: report of a survivor
Irish Med J 1976; 69 : 435-438.
- 56 MALCOLMSON E, BEESLEY J, Unsuccessful immunosuppressant treatment of paraquat poisoning. Brit Med J; 3 : 650-651
- 57 FITZGERALD G R, BARNIVILLE G, FITZPATRICK P, EDWARDS A, SILKE B, Adrenal abnormalities in paraquat poisoning: an indication for corticosteroid therapy. Irish J Med Sci 1977; 146 : 421-423
- 58 FISHER H K, CLEMENTS J A, WRIGHT R R, The enhancement of oxygen toxicity by the herbicide paraquat. Am Rev Resp Dis 1978; 107 : 246
- 59 KEHRER J P, HASCHECK W, WITSCHI H P, The influence of hyperoxia on the acute toxicity of paraquat and diquat, Drug Chem Toxicol 1979; 2 : 397-408
- 60 PRATT I S, KEELING P L, SMITH L L, The effects of high concentrations of oxygen on the toxicity of paraquat and diquat in rats. Toxicol Appl Pharmacol 1979; 48 : 459
- 61 MONTGOMERY M R, WYATT I, SMITH L L, Oxygen effects on the metabolism and paraquat uptake in rat lung slices. Expo Lung Res 1980; 1 : 239-250
- 62 WARDEN J A, RHODES M L, The failure of hypoxia to protect against paraquat toxicity in rats. Am Rev Resp Dis 1978; 117 : 265

- 63 SMITH L L, ROSE M S, The effects of low oxygen therapy on paraquat toxicity in rats. In: Toxicology as a Predictive Science Plaa G L, Duncan WAM, eds. New York, Academic Press 1978; 443
- 64 RHODES M L, ZAVALA D C, BROWN D, Hypoxic protection in paraquat poisoning. Lab Invest 1976; 35 : 496
- 65 VAN DIJK A, MAES R A A, DROST R H, DOUZE J M C, VAN HEIJST A N P, Paraquat poisoning in man. Arch Toxicol 1975; 34 : 129-136
- 66 DOUZE J M C, VAN DIJK A, GIMBRERE J S F, VAN HEIJST A N P, MAES R A A, Intensive therapy after paraquat intoxication In: Clinical Aspects of Paraquat Poisoning. Fletcher K, ed. London, ICI Ltd 1977. 34-45
- 67 DOUZE J M C, VAN HEIJST A N P, Paraquat intoxication: oxygen the real problem. Acta Pharmacol Toxicol 1977; 41 Suppl 11 : 241-245

SECTION 4

CONCLUDING OBSERVATIONS

4 CONCLUDING OBSERVATIONS

It is always easy to be wise after the event and it seems clear that the manufacturers of paraquat as a herbicide did not anticipate any exceptional problems with this compound when it was first introduced onto the market during the mid-1960s. In retrospect, however, it should perhaps have been expected that some serious accidents would occur with a herbicide of relatively high toxicity and in particular one with the type of toxic properties that pre-registration animal studies would have uncovered. It has to be remembered that farm workers are notoriously careless and often exhibit little safety consciousness. In general, however, the incidence of serious accidents in occupational use appears to have been very low, as has been discussed earlier. On the other hand there have been a large number of deaths as a result of accidental or deliberate ingestion of paraquat formulations.

This short section will attempt to draw some conclusions from the data provided in the earlier parts of this thesis in relation to the two situations of paraquat use in agriculture and paraquat misuse in accidental and, more particularly, deliberate poisoning.

4.1 PARAQUAT IN USE

The main conclusions to be drawn from the available published data, together with the results of the author's three studies of paraquat occupational use situations, have been discussed broadly in Section 2.5. The data would indicate that neither the formulation of paraquat as commercial preparations, nor the standard higher volume spraying at concentrations of up to 0.5% paraquat ion (1:40 dilution of 'Gramoxone') are likely to pose any significant risk to worker health.

The importance of these studies lies, in part at least, in the long period of occupational exposure which the formulation workers and Malaysian spray operators had experienced. It is thus worth re-emphasising that in spite of such long and continuous occupational exposure associated with significant dermal contamination, there were no reports of any symptoms that would point to significant absorption of paraquat. More importantly, as far as the group of spray workers was concerned, a wide range of clinical measurements failed to show any variation from the values that were found in the unexposed control populations. It may therefore be reasonably affirmed that paraquat does not constitute a significant risk to health under proper conditions of manufacture and use.

It was noted earlier, however, that the use of low volume/high concentration spraying raised very real problems. Exposure to concentrations not greatly in excess of those

used in the Thailand trial have since been reported as causing fatalities through percutaneous absorption^{1,2}.

The results of that particular study would strongly indicate that the practice of low volume spraying, using hand-held equipment, is a dangerous practice which increases the level of risk to the sprayman to totally unacceptable degrees.

Unfortunately, the label instructions on ICI Ltd formulations did not, in the past, make it clear that there was any consideration of safety to be taken into account in deciding on the dilution for spraying. A range of dilutions was set out, but these related to herbicidal efficacy not to matters of safety. Partly as a result of the Thailand work reported in this thesis, ICI Ltd have now clarified their label instructions and have placed a clear limit for the upper spray strength to be used with hand-held sprayers (1:40 dilution of the 20% agricultural concentrate) (see table 2.1, p 49). Considerable amounts of the older formulations, however, are still likely to be in use around the world.

4.2 PARAQUAT IN MISUSE

The real problem with regard to paraquat relates to its misuse in cases of accidental or deliberate poisoning. The existing controls on the sale of the agricultural concentrate in the United Kingdom have done much to reduce the incidence of accidental poisonings. On the other hand, the evidence for 'illicit' sales and the apparent ease with which commercial formulations were obtained by those not entitled to them, as discussed earlier in the thesis (Section 3.3.2), must raise considerable concern. It seems likely that the voluntary registration scheme devised by the British Agrochemicals Association for distributors will go a long way towards reducing the sale of scheduled materials to the general public (Major C S, 1981, personal communication), but clearly if such voluntary means fail, there will be a need for a tighter statutory control and inspection system to ensure the proper regulation of the sale of scheduled pesticides.

The evidence from the author's series of cases reported here and from the only published data dealing specifically with retail granular formulations³, would indicate that these preparations present no significant risk of fatal accidental poisoning, although they are being increasingly used for deliberate self-poisoning. The mortality, however, is low in such cases and the actual dose of paraquat taken is frequently very small indeed. In view of this situation it would seem to be a gross over-reaction to ban the use of paraquat in those garden and retail formulations specifically designed for domestic use. On the other hand, in those

countries (such as Eire, Japan and Western Samoa) where liquid agricultural concentrates are more freely available than they are in the United Kingdom and where self-poisoning is a significant problem, then there is a strong case for the manufacturer to introduce measures which may help in reducing fatalities from self-poisoning. In total numbers, 20 or 30 deaths each year from paraquat self-poisoning in Western Samoa may appear small, especially in the world-wide terms in which large companies think, but in terms of a population only the size of Oxford, the problem changes in significance considerably.

The very small range of dose for which any treatment is likely to be effective has not always been sufficiently recognised. The great weight of evidence, discussed earlier, would indicate that the only cases likely to be saved with any degree of probability are those who have:

- (a) ingested less than 5g of paraquat ion,
- (b) had treatment instituted within 2 hours of ingestion, and
- (c) show plasma paraquat levels not exceeding 2mg/litre at four hours after ingestion.

The dose of 5g paraquat ion represents but 25ml of 'Gramoxone', literally 'a mouthful'. There are very few other compounds in general use where there is such a sharp 'cut off' between treatable and fatal doses and any measure which can be introduced which will extend that boundary should be given careful consideration, especially in view of the 'cry for help' cases whose self-poisoning is no more than a suicidal gesture. This is an important group of poisoning cases who often take

what they believe to be a 'small' dose (a mouthful, for example), but which in the case of paraquat turns out to be inevitably fatal. One recent estimate suggests that as many as three quarters of self-poisonings are 'impulse' cases of this type ⁴.

The benefits of paraquat in agricultural practice have been demonstrated over the past twenty years, but in common with most benefits there are associated risks and dangers. It may be used with safety, but it may also be misused with dire results. Good and evil are rarely far apart in this world and it requires vigilance and a willingness to act to ensure the continuing good. It was, after all, but a league between Mount Gerizim and Mount Ebal ⁵.

4.3. REFERENCES

- 1 JAROS F, Acute percutaneous paraquat poisoning.
Lancet 1978; 1 : 275
- 2 LEVIN P J, KLAFF L J, ROSE A G, FERGUSON A D,
Pulmonary effects of contact exposure to paraquat:
a clinical and experimental study. Thorax 1979; 30 :
150-160.
- 3 FITZGERALD G R, BARNIVILLE G, Poisoning by granular
paraquat. J Irish Phys Surg 1978; 7 : 133-136
- 4 KESSEL W I N, Self poisoning II. Brit Med J 1965; 2 :
136-140
- 5 DEUTERONOMY 11:29

SECTION 5

SELECT BIBLIOGRAPHY

5 SELECT BIBLIOGRAPHY

The literature on paraquat is immense with something in the order of 1200 publications relating to the matters discussed in this thesis. The accompanying bibliography is thus in no sense complete, being merely a supplement to the specific references for each section of the thesis. The bibliography lists only papers, review articles etc related to the human toxicity and treatment, general toxicology, biochemistry (including toxic mechanisms) and the ecotoxicology of paraquat. The references are set out by year of publication and in alphabetical order of authors. Foreign language papers are included and the language of the publication is noted. Where English abstracts of foreign papers are available, these are noted in relation to the original paper. There are a great many publications of individual cases of poisoning, autopsy results etc. Only a representative sample of these is included in the bibliography.

• 1960

Homer RF, Mees GC & Tomlinson TE
 Mode of Action of Dipyridyl Quaternary Salts as Herbicides.
J Sci Food Agric 11;309-315:1960

• 1962

Calderbank A & Crowdus SH
 Bipyridyl Herbicides
Reports on Progress of Appl Chem 47; 536-42:1962

• 1963

Hopkins DP
 Pest Control Chemicals
Mfg Chem 34; 269:1963

• 1964

Calderbank A
 Mode of Action of the Bipyridylum Herbicides, Diquat and Paraquat.
Seventh British Weed Control Conference 1; 312-320:1964

Holden AV
 The Possible Effects on Fish of Chemicals used in Agriculture.
J Inst Sew Purif No.4; 361:1964

Tarakhovskii ML & Gilenson AE
 Pharmacology of New-Bis-Quaternary Derivatives of Bipyridine.
[Farmakol i Toksikol (Kiev: Zdorov's) Sb No.1; 67-73 : 1964](Russ)
Chem Abstr 64; 4101h:1966

Webbe G & Sturrock RF
 Laboratory Tests of Some New Molluscicides in Tanganyika
[Ann Trop Med Parasitol 58(2); 234-9]
Chem Abstr 61; 1528g:1964

• 1965

Cope OB
 Some Responses of Fresh-water Fish to Herbicides.
Proc S Weed Conf 18; 439-45 : 1965

Hassall KA
 Pesticides: Their Properties, Uses and Disadvantages. II.
 Fungicides and Herbicides. Pesticides in Relation to Man
Brit Vet J 121; 199:1965

Howe DJT & Wright N
 The Toxicity of Paraquat and Diquat.
Proc 18th NZ Weed and Pest Control Conference ; 105-14 : 1965

Newman JF
 Methods of Assessing Wild Life Hazards.
Proc Br Insecticides & Fungicides Conf; 342-57:1965

• 1966

Paraquat and Diquat spring to Life. (Review)
BIBRA Inf Bull 5;486-7:1966.

Bullivant CM

Accidental Poisoning by Paraquat: Report of Two Cases in Man.
Br med J 1;1272-3:1966

Clark DG, McElligott TF & Weston Hurst E
The Toxicity of Paraquat.
Br J ind Med 23;126-132:1966

Daniel JW & Gage JC

Absorption and Excretion of Diquat and Paraquat in Rats.
Br J ind Med 23;133-136:1966

Newman JF & Way JM

Some Ecological Observations on the Use of Paraquat and Diquat
as Aquatic Herbicides.

Proc Br Weed Control Conf ; 582-4:1966

Stevens MA & Walley JK

Tissue and Milk Residues arising from the Ingestion of Single
Doses of Diquat and Paraquat in Cattle.

J Sci Food Agric 17;472-5:1966

Zakrividoroga SP, Nevskaia TL, Gruzdev AI & Zakrividoroga ZS.

Toxicology and Pharmacology of Gramoxone Salts.

[Gig Toksikol Pestits Klin Otravlenii No 4; 206-13:1966] (Russ)
Chem Abstr 69;58514:1968

• 1967

The Bipyridilium Story continued (review)

BIBRA Inf Bull 6;443-444:1967

Poisoning from Paraquat. (editorial)

Br med J 3;690-691:1967

Alekperov UK, Kolomiets AF & Shcherbakov VK

The Antimutagenic Activity of Paraquat.

Dokl Acad Nauk 176;199-201:1967

Almog Ch & Tal E

Death from Paraquat after Subcutaneous Injection.

Br med J 3;721:1967

Dunachie JF & Fletcher WW

Effect of some Herbicides on the Hatching Rate of Hen's Eggs.

Nature 215;1406-7: 1967

Fletcher K

Production and Viability of Eggs from Hens treated with Paraquat.

Nature 215;1407-8: 1967

Manktelow BW

The Loss of Pulmonary Surfactant in Paraquat Poisoning: A Model
for the Study of the Respiratory Distress Syndrome.

Br J exp Path 48;366-9:1967

• 1967 (cont)

McIntosh IG
 Herbicides and their Toxicity to Livestock.
NZ vet J 15;70-2:1967

Mourin KA
 Paraquat Poisoning.
Br med J 4;486:1967

Palmer PC
 Liveweight Gains of Young Sheep grazing Chemically Treated Pastures.
Proc 20th NZ Weed and Pest Control Conf; 50:1967

Siver PYa
 The Effect of some Toxic Chemicals on the Distribution of Sulphur-35
 in Tissues and Organs of Albino Rats.
 [Gig Tr Prof Zabol 11(9); 51-2:1967] (Russ)
Chem Abstr 68;28129:1968

Swan AAB
 Paraquat Poisoning.
Br med J 4;551:1967

Swan AAB
 Toxicological Problems in the Control of Water Weeds.
 European Weed Research Council. Proceedings of the 2nd Aquatic Plants Symposium 22-24 Aug. 1967 Oldenburg

Yeo RR
 Dissipation of Diquat and Paraquat and Effects on Aquatic
 Weed and Fish.
Weeds 15;42-46:1967

• 1968

Keep an Eye on those Dipyridiliums (review)
BIBRA Inf Bull 7;464-5:1968

More on Dipyridilium Toxicity (review)
BIBRA Inf Bull 7;526-7:1968

Akhavein AA & Linscott DL
 The Dipyridilium Herbicides, Paraquat and Diquat.
Residue Rev 23;97-145:1968

Barnes JM
 Poisons that Hit and Run.
New Scient 38;619-620:1968

Baynova A & Salambachev L
 A Study of the Functional State of the Thyroid Gland under
 Intoxication with Dipyridiliums by means of Radioactive Iodine.
Dokl Bolg Akad Nauk 21;841-3: 1968 (Bulgarian)

Bronkhorst FB, Van Daal JM & Tan HD
 Fatal Poisoning with Paraquat (Gramoxone)
Ned Tijdschr Geneesk 112;310-3:1968 (Dutch)

• 1968 (cont)

Calderbank A
The Bipyridilium Herbicides
Adv Pest Control Res 8;127-235:1968

Calderbank A, McKenna RH, Stevens MA & Walley JK
Grazing Trials on Paraquat-treated Pasture.
J Sci Food Agric 19;246-50:1968

Campbell S
Paraquat Poisoning.
Clin Toxicol 1;245-9:1968

Campbell S
Death from Paraquat in a Child
Lancet 1;144:1968

Cant JS & Lewis DRH
Ocular Damage due to Paraquat and Diquat.
Br med J 2;224:1968

Cant JS & Lewis DRH
Ocular Damage due to Paraquat and Diquat.
Br med J 3;59:1968

Cooper P
Quarterly reviews. Current Aspects of Toxicology.
Pharm J 200;595-8:1968

Duffy BS & O'Sullivan DJ
Paraquat Poisoning
J Ir med Ass 61;97-8:1968

Fennelly JJ, Gallagher JT & Carroll RJ
Paraquat Poisoning in a Pregnant Woman.
Br med J 3;722-723:1968

Gage JC
The Action of Paraquat and Diquat on the Respiration of Liver
Cell Fractions.
Biochem J 109;757-761:1968

Gage JC
Toxicity of Paraquat and Diquat Aerosols generated by a
Size-selective Cyclone. Effect of Particle Size Distribution.
Br J Ind Med 25;304-314:1968

Gage JC
Further Observations on the Determination of Paraquat
and Diquat.
Bull Int Ass Forensic Toxicol 5(3);11:1968

Herczeg von E & Reif A
Pulmonary changes in Fatal Paraquat Poisoning.
Zbl Alig Path 111;325-8:1968 (Ger)

Kerr F, Patel AR, Scott PDR & Tompsett SL
Paraquat Poisoning treated by Forced Diuresis.
Br med J 3;290-1:1968

• 1968 (cont)

Khera KS & Whitta LL.
 Embryopathic effects of Diquat and Paraquat in the Rat.
Ind Med Surg 37;553:1968

Matthew H, Logan A, Woodruff MFA & Heard B
 Paraquat Poisoning-lung Transplantation.
Br med J 3;759-763:1968

McKean WI
 Recovery from Paraquat Poisoning.
Br med J 3;292:1968

O'Dwyer WF & Woodcock J
 Paraquat Poisoning (Toxicological Case Records - Goulding R)
Practitioner 200;739:1968

Oreopoulos DG, Soyannwo MAO, Sinniah R, Fenton SSA, McGeown MG
 & Bruce JH
 Acute Renal Failure in Case of Paraquat Poisoning.
Br med J 1;749-750:1968

Swan AAB
 Ocular Damage due to Paraquat and Diquat.
Br med J 2;624:1968

Swan AAB
 Ocular Damage due to Paraquat and Diquat.
Br med J 3;187:1968

Tilling W
 Paraquat Intoxication.
Dt med Wschr 93;2439-41:1968.(Ger)

Treating paraquat poisoning.
Pharm J 201; 627 : 1968.

• 1969

Death from Paraquat (editorial)
British Medical Journal 4;817:1969

Nail Damage from Paraquat and Diquat (review)
BIBRA Inf Bull 8; 269-270:1969

Alabaster JS
 Survival of Fish in 164 Herbicides, Insecticides, Fungicides,
 Wetting Agents and Miscellaneous Substances.
Int Pest Contr 11; 29-35:1969

Bainova A
 Chronic Oral Toxicity of Dipyridyl Herbicides
 (Khigiena i Zdraveopazvane 12;325-332:1969) (Russ)
 WHO Information Circular on the Toxicity of Pesticides to Man.
 VBC/TOX/69.4 p25 1969

• 1969 (Cont)

Bainova A & Anadolüska A
Changes in the Acid-base Metabolism in Acute Paraquat Intoxication.
Cr Acad bulg Sci 22; 221-4:1969 (Bulgarian)

Carson ED
Fatal Paraquat Poisoning
Bull int Ass Forensic Toxicol 6 (2); 4:1969

Comment FJ
Poisoning by Oral Ingestion of the Herbicide Gramoxone.
(Prakt Lek 49; 911-912:1969) (Polish)
Chem Abstr 73; 12673:1970

Conning DM, Fletcher K & Swan AAB
Paraquat and related Bipyridyls (review article)
Br med Bull 25; 245-9:1969

de Larrard J
Poisoning in an Agricultural Worker by a Quaternary Ammonium Compound (Gramoxone)
Archs Mal prof Med Trav 30; 421:1969 (French)

Fisher HK & Clements JA
Effects of the Herbicide Paraquat on Mechanical Properties of Rat Lungs.
Fed Proc Fed Am Soc exp Biol 28; Abstr 1481: 1969

Gage JC
Some Aspects of the Toxicity of Paraquat.
Weed Res 9; 375-6: 1969

Gage JC
Some Aspects of the Toxicity of Paraquat.
Meded Rijksfak Landbouwwetensch, Gent 34; 392-400: 1969 (Dutch)

Gaines TB
Acute Toxicity of Pesticides
Toxic appl Pharmac 14; 515-34: 1969

Guardascione V & di Bosco MN
A Contribution to the Knowledge of Professional Pathology from Paraquat, a Herbicide based on Dipyridyl.
Folia Med Napoli 52; 728-38: 1969 (Italian)

Hargreave TB Gresham GA & Karayannopoulos S
Paraquat Poisoning
Postgrad med J 45; 633-5:1969

Heyndrickx A, Schepens P & Scheiris Ch
Toxicological Analysis of a Fatal Poisoning by Paraquat.
Eur J Toxicol 2; 178-80: 1969

Joyce M
Ocular Damage caused by Paraquat.
Br J Ophthal 53; 688-690: 1969

• 1969 (Cont)

Kalbfleisch H

Pathological and anatomical findings in cases of poisoning by the herbicide Gramoxone (paraquat).

Klin Wschr 47; 286:1969 (German)

Khera KS & Clegg DJ

Perinatal Toxicity of Pesticides.

Can med Ass J 100; 167-172: 1969

Lanzinger G, Ritz E, Franz HE, Kuhn HM & Klein H

Acute Interstitial Pulmonary Fibrosis in Paraquat Poisoning.

Clinico-anatomical Observations of a Case with Fatal Outcome.

Munch med Wschr 111; 944-9: 1969 (German)

Lloyd E L.

Recovery after taking Weedol.

Br med J 2; 189: 1969

Mathew H

Paraquat Poisoning Lung Transplant.

Eur J Toxicol 197: 1969

Mracek J & Krch V

Oral Poisoning with the Herbicide "Gramoxone".

Prakt Lek 49; 172-173: 1969 (Polish)

Peyresblanques MJ

Ocular burns caused by Gramoxone

Bull Soc Ophthalmol 69; 928:1969

Samman PD & Johnston ENM

Nail Damage Associated with handling Paraquat and Diquat.

Br med J 1; 818-9: 1969

Schleuter M

Determination of Fish Toxicity of Substances in the Water and the Toxic Threshold of Herbicides.

(Zt Fisch Hilfswiss 17; 457-71: 1969) (Ger)

Chem Abstr 73; 108597: 1970

Styles JA & Conning DM

The Stimulation of Fibroplastic Proliferation by Killed Macrophages in vitro.

Proc Path Soc Gt Britain & Northern Ireland 67 (26); 10: 1969

Swan AAB

Exposure of Spray Operators to Paraquat.

Br J Ind Med 26; 322-9: 1969

Tompsett SL

Paraquat Poisoning (Non-fatal)

Bull Int Ass Forensic Toxicol 6 (2); 4-5: 1969

Weidenbach J

Paraquat Poisoning

Dtsch med Wschr 94 547-9 1969

• 1970

Anon

An Eyeful of Paraquat (review)
BIBRA Inf Bull 9; 254 : 1970

Anderson CG

Paraquat and the Lung
Aust Radiol 14; 409-11: 1970

Beyer KH

The Analytical Determination and Toxicology of Paraquat.
Dt ApothZtg 110; 633-5 : 1970 (German)

Brown SS & Gibson PF

Paraquat Toxicity

Br med J 4; 114 : 1970

Cambar PJ & Aviado DM

Brencho Pulmonary Effects of Paraquat and Expectorants.
Archs environ Hlth 20; 488-494: 1970

Clements JA & Fisher HK

The Oxygen Dilemma.

New Engl J Med 282; 976-7 : 1970

De Lavaur E & Carpenter Le Sech J

Presence of Pesticides in the Wild Animals of France.

(Phytiat-Phytopharm 19; 55-63 : 1970) (French)

Chem Abstr 75; 62534 : 1971

Dunachie JF & Fletcher WW

The Toxicity of Certain Herbicides to Hen's Eggs assessed by
 the Egg Injection Technique.

Ann appl Biol 66; 515-20 : 1970

Fisher HK, Clements JA & Tierney DF

Early Pulmonary Effects of Paraquat in Rats.

Clin Res 18; 190 : 1970

Fitzgerald O, McGeeney KF & Gilhooly B

Serum Trypsin Inhibitor and Paraquat.

Br med J 4; 747-8 : 1970

Fletcher K & Swan AAB

Paraquat Toxicity

Br med J 3; 646-7 : 1970

Fletcher K & Wyatt I

The Composition of Lung Lipids after Poisoning with Paraquat.

Br J exp Path 51; 604-610 : 1970

Hall RA & Carson ED

Fatal Paraquat Poisoning

Bull int Ass Forensic Toxicol 7; 5 : 1970

• 1970 (Cont)

Ivemark B, Robertson B, Enhörning G, Malmqvist E & Modee J
 Paraquat Poisoning as an Experimental Model of Idiopathic Respiratory Distress.
J Path 101 (4); p.iii : 1970

Ivemark B, Robertson B, Enhörning G, Malmqvist E, Mcdee J
 Paraquat-induced respiratory distress in the rat
Acta Path Microbiol Scand 78; 495 : 1970

Kimbrough RD & Gaines TB
 Toxicity of Paraquat to Rats and its Effect on Rat Lung.
Toxic appl Pharmac 17; 679-690 : 1970

Masterson JG & Roche WJ
 Another Paraquat Fatality
Br med J 2; 482 : 1970

Masterson JG & Roche WJ
 Fatal Paraquat Poisoning.
J Ir med Ass 63; 261-4 : 1970

McDonagh BJ & Martin J
 Paraquat Poisoning in Children
Archs Dis Child 45; 425-7 : 1970

Robertson B, Ernhörning G, Ivemark B, Malmqvist E & Modee J.
 Paraquat-induced Derangement of Pulmonary Surfactant in the Rat.
Acta Paediat Scand 59 Suppl; 37-39 : 1970.

Smalley HE & Radeleff RD
 Comparative Toxicity of the Herbicide Paraquat in Laboratory and Farm Animals.
Toxic appl Pharmac 17; 305 : 1970

Stokes DM & Walker DA
 Paraquat Toxicity
Br med J 3; 462-3 : 1970

Stroev VS
 The Cytogenic Activity of the Herbicides Atrazine, Chloro-IPC and Paraquat.
Genetica 6 (3); 31-37 : 1970

Tompsett SL
 Paraquat Poisoning - Fatal
Bull int Ass Forensic Toxicol 7; 4 : 1970

Tompsett SL
 Paraquat Poisoning
Acta pharmac tox 28; 346-358 : 1970

• 1970 (Cont)

Toner PG, Veters JM, Spiling WGS & Harland WA
 Fine Structure of the Lung Lesion in a Case of Paraquat
 Poisoning.

J Path 102; 182-5 : 1970

Verbetskii VE & Stolyarchuk AA

Toxicological and Pharmacological Properties of Herbicides which
 are Bipyridine Derivatives - Gramoxone and Reglone.
(Vop Gig Toksikol Pestits Tr Nauch Sess Akad Med Nauk SSSR ; 164-8 : 1967
 Publ 1970) (Russian)
Chem Abstr 74; 110708 : 1971

Vijeyaratnam GS & Corrin B
 Experimental Paraquat Poisoning
J Path 101;

Walker DA & Stokes DM
 Paraquat Toxicity
Br med J 4; 243 : 1970

• 1971

Anon
 Paraquat Poisoning
Lancet 2; 1018-9 : 1971

Paraquat Poisoning: Clinicopathological Conference.
Scot med J 16; 407-421 : 1971

Ayers L & Tierney D
 High PO₂ and Pentose Phosphate Pathway in Rat Lungs.
Clin Res 19; 190:1971

Ayers L, Tierney DF
 Pentose Pathway: A possible metabolic mechanism to protect
 the lung from a high PO₂
Am Rev Resp Dis 103; 906 : 1971

Barber PJ
 Accidental Vaccination with Paraquat
Br med J 2; 768:1971

Beebejaun AR, Beevers G & Rogers WN
 Paraquat Poisoning - Prolonged Excretion.
Clin Toxicol 4; 397-407 : 1971

Billewicz-Stankiewicz J & Pawlowski L
 The Effect of Gramoxone on the Activity of the Nervous
 System of Laboratory Animals
 (Bromat Chem Toksykol 4; 287-92 : 1971) (Polish)
Chem Abstr 76; 81904 : 1972

• 1971 (Cont)

Bony D, Favarel-Garrigues JC, Cledes J, Cambeilh J & Castaing R
 Paraquat Poisoning
Eur J Toxicol IV; 406-11: 1971

Brooks RE
 Ultrastructure of Lung Lesions produced by Ingested Chemicals.
 I. Effect of the Herbicide Paraquat on Mouse Lung.
Lab Invest 25; 536-45: 1971

Browne TD
 Treatment of Paraquat Ingestion
Br med J 3; 580: 1971

Brzeski Z, Krupa A & Czuczwar Z
 A Fatal Case of Poisoning by Dipyridyl Herbicide - Gramoxone.
Pol Tyg Lek 26; 1368-9: 1971 (Polish)

Butler C & Kleinerman J
 Paraquat in the Rabbit
Br J ind Med 28; 67-71: 1971

Clark DG
 Inhibition of the Absorption of Paraquat from the
 Gastrointestinal Tract by Adsorbents.
Br J ind Med 28; 186-8: 1971

Cole AJL, Hawkins JB & Mayer PP
 Control of Paraquat (Letter to the Editor)
Br med J 3; 110: 1971

Davidson CL & Papirmeister B
 Bacteriostasis of Escherichia coli by the herbicide paraquat
Proc Soc exp Biol Med 136; 359-364: 1971

Dimov D
 Diagnosis and treatment of paraquat poisoning
Arch Hyg Rada Toks 32; 184-6: 1971

Dodge AD
 The Mode of Action of the Bipyridylum Herbicides, Paraquat and
 Diquat.
Endeavour 30; 130-5: 1971

Earnest RD
 The Effect of Paraquat on Fish in a Colorado Farm Pond.
Progve Fish Cult 33; 27-31: 1971

Fennelly JJ, Fitzgerald MX & Fitzgerald O
 Recovery from Severe Paraquat Poisoning following Forced
 Diuresis and Immunosuppressive Therapy.
J Ir med Ass 64; 69-71: 1971

Ferguson DM
 Renal Handling of Paraquat.
Br J Pharmac 42; 636P: 1971

• 1971 (Cont)

Fisher HK, Humphries M & Bails R
Paraquat Poisoning: Recovery from Renal and Pulmonary Damage.
Ann intern Med 75; 731-6 : 1971

Fowler BA & Brooks RE
Effects of the Herbicide Paraquat on the Ultrastructure
of the Mouse Kidney.
Am J Path 63; 505-20 : 1971

Grabensee B, Veltmann G, Mürtz R & Borchard F
Poisoning by Paraquat.
Dt med Wschr 96; 498-506 : 1971 (German)

Grundies H, Kolmar D & Bennhold I
Paraquat Poisoning: Casuistics, with Special Consideration
of Haemodialysis.
Dt med Wschr 96; 588-9 : 1971 (German)

Hearn CED & Keir W
Nail Damage in Spray Operators exposed to Paraquat
Br J Ind Med 28; 399-403 : 1971

Hensel G & Dürr F
Dialysis Therapy for Paraquat Poisoning
Medsche Welt 22; 1790-4 : 1971 (German)

Iff HW, Brewis RAL, Mallick NP, Mawer GE, Orr WMcN & Stern MA
Paraquat Poisoning.
Schweiz med Wschr 101; 84-8 : 1971

Malone JDG, Carmody M, Keogh B & O'Dwyer WF
Paraquat Poisoning - A Review of Nineteen Cases.
J Ir med Ass 64; 59-68 : 1971

Mickelson KNP & Fulton DB
Paraquat Poisoning treated by Replacement Blood Transfusion.
NZ med J 74; 26-7 : 1971

Minarik F, Dostal J, Neuwirt V, Pohlidalova L
Gramoxone Poisoning
Prakt Lek 51; 360-3 : 1971

Modee J, Ivemark B, Robertson B
Ultrastructure of the alveolar epithelium and the
alveolar lining layer in paraquat-induced experimental
respiratory distress
Acta Path Microbiol Scand 79; 311 : 1971

Nienhaus H & Ehrenfeld M
Pathogenesis of Lung Disease in Paraquat Poisoning
Beitr Path 142; 244-267 : 1971 (German)

• 1971 (Cont)

Pasi A & Hine CH
Paraquat Poisoning.
Proc West Pharmacol Soc 14; 169-172: 1971

Robertson B, Enhörning G, Ivemark B, Malmqvist E & Modee J
Experimental Respiratory Distress induced by Paraquat.
J Path 103; 239-44: 1971

Smith P
A Light and Electron-microscopic study of the pulmonary lesions induced
in rats by paraquat
J Path 104; p VII: 1971

Vijeyaratnam GS & Corrin B
Experimental Paraquat Poisoning : A Histological and Electron-
Optical Study of the Changes in the Lung
J Path 103; 123-9: 1971

Von der Hardt H & Cardesa A
Early histopathological alterations following paraquat
intoxication
Klin Wschr 49; 544-550: 1971 (German)

Wanic W, Mrciniak J, Sikorski M & Dabrowski H
A case of lethal poisoning by Gramoxone
Pol Tyg Lek 26; 1166-68: 1971 (Polish)

• 1972

Anon
Touching up the Paraquat Picture
BIBRA Inf Bull 11; 176-81: 1972

Anon
Paraquat Poisoning
Vet Record Inf Suppl No. 106; pp 95-6: Dec 1972

Toxicity hazards of herbicides to livestock
Planters Bull 122; 181-2: 1972
(Hlth Asp Pest Bull 6; 73-2225: 1973)

Anderson KJ, Leighty EG & Takahashi MT
Evaluation of Herbicides for possible mutagenic properties.
J Agric Fd Chem 20; 649-656: 1972.

Araki S, Ushio K & Iwabuchi T
A Case History and Autopsy Findings in Acute Poisoning
by the Herbicide Gramoxone.
(Nippon Saigai Igakukai Kaishi 20; 43-44: 1972) (Japan)
(Hlth Asp Pest 5; 72-1694: 1972)

Bainova A, Zlateva M & Vulcheva VI
Chronic Inhalation Toxicity of Dipyridylum Herbicides.
(Khig Zdraveopazvane 15; 25-31: 1972) (Russian)
Chem Abstr 77; 110242: 1972

• 1972 (Cont)

Bainova A, Valcheva V

Experimental substantiation of gramoxone mac in working areas.

Trudove Nauch 23; 71-75 : 1972 (Russian)

Burman D, Hodson AK & Mott MG

Paraquat Poisoning

Lancet 1; 201 : 1972

Calderbank A

Environmental Considerations in the Development of

Diquat and Paraquat as Aquatic Herbicides.

Outlook Agr 7; 51-4 : 1972

Carson ED

Fatal Paraquat Poisoning in Northern Ireland

J forens Sci Soc 12; 437-443 : 1972

Castaing MR, Bony D, Haglund P, Cledes J, Bourzai M & Cambeilh J

Paraquat Poisoning

Bordeaux Med 5; 1577-1582 : 1972 (French)

Chao TC

Paraquat Poisoning

Ann Acad Med 1; 68-73 : 1972

Davidson JK & Macpherson P

Pulmonary Changes in Paraquat Poisoning.

Clin Radiol 23; 18-25 : 1972

Favarel-Garrigues JC

Acute Pulmonary Fibrosis by Ingestion of a Herbicide containing
Paraquat.

Bull Physio-Pathol Resp 8; 1289-1294 : 1972 (French)

Fletcher K & Wyatt I

The Action of Paraquat on the Incorporation of Palmitic Acid
into Dipalmitoyl Lecithin in Mouse Lungs.

Br J exp Path 53; 225-230 : 1972

Galloway DB & Petrie JC

Recovery from Severe Paraquat Poisoning

Postgrad med J 48; 684-686 : 1972

Gardiner AJS

Pulmonary Oedema in Paraquat Poisoning.

Thorax 27; 132-5 : 1972

Harrison LC, Dortimer AC & Murphy KJ

Fatalities due to the Weed-killer Paraquat.

Med J Aust 2; 774-779 : 1972

Hofman A & Frohberg H

Gramoxone Poisoning in the Federal Republic of Germany.

Dtsch med Wschr 97; 1299-1303 : 1972 (German)

• 1972 (Cont)

Matthew H
Paraquat and the Lung.
Ann Intern Med 76; 835: 1972

McElligott TF
The Dermal Toxicity of Paraquat: Differences due to Techniques of Application.
Toxic appl Pharmac 21; 361-8 : 1972

Modeé J, Ivemark BI & Robertson B
Ultrastructure of the Alveolar Wall in Experimental Paraquat Poisoning.
Acta path microbiol Scand 80; 54-60:1972

Moriyama I, Ichikawa H & Ide H
Death after Accidental Ingestion of Gramoxone resulting in Fibrosis of the Lung.
[Nippon Noson Igakkai Zasshi 21; 244-245:1972] (Japan)
Hlth Asp Pest 6; 73-347: 1973

Murray RE & Gibson JE
A Comparative Study of Paraquat Intoxication in Rats, Guinea-pigs and Monkeys.
Exp Mol Pathol 17; 317-325:1972

Musti M
Fatal Acute Haemolytic Anaemia and Acute Toxic Hepatopathy from Paraquat.
Folia Med 55; 51-55:1972 [Ital]

Okada H, Kamata T, Nakagawa A & Hirakawa M
A Case of Acute Poisoning caused by Gramoxone.
[Nippon Kyobu-Geka Gakkai Zasshi 10(suppl); 55:1972] (Japan)
Hlth Asp Pest 5; 72-1897:1972

Okada H, Kamata T, Nakagawa A & Hirakawa S
A Case of Acute Intoxication due to Paraquat Dichloride.
[Nippon Kyobu Shikkan Gakkai Zasshi 10(12); 673 : 1972] (Japan)
Hlth Asp Pest 6; 73-1103:1973

Pape KSSB
Paraquat Poisoning
Ned Tijdschr Geneesk 116; 199:1972 (Dutch)

Sharp CWM, Ottolenghi A & Posner HS
Correlation of Paraquat Toxicity with Tissue Concentration and Weight Loss of the Rat.
Toxic appl Pharmac 22; 241-251:1972

Shinoda H, Ito K, Matsunaga T, Takada T & Nomura T
Two Suicides by Acute Pesticide Intoxication.
[Nippon Noson Igakkai Zasshi 21; 242-3:1972] (Japan)
Hlth Asp Pest 6; 73-0081:1973

- 1972 (cont)

Uetake S, Yamada K, Seta K, Shirokura T, Maekawa T,
Shigitani R, Ogura H, Satane B & Toyoda O.
A Case of Gramoxone Intoxication.
(Nippon Naika Gakkai Zasshi 61 : 1435-6 ; 1972) (Japan)
Hlth Aspt Pest 6 ; 73-0855 : 1973

Wasan SM & McElligott TF
An Electron Microscopic Study of Experimentally induced
Interstitial Pulmonary Fibrosis.
Am Rev resp Dis 105 ; 276-82 : 1972

Wright KA & Cain RB
Microbial Metabolism of Pridinium Compounds: Metabolism of
4-Carboxy-1-methylpyridinium Chloride, a Photolytic Product of
Paraquat.
Biochem J 128 ; 543-59 : 1972

Wright KA & Cain RB
Microbial Metabolism of Pyridinium Compounds: Radioisotope
Studies of the Metabolic Fate of 4-Carboxy-1-methylpyridinium chloride.
Biochem J 128 ; 561-8 : 1972

- 1973

Bainova A, Zlateva M, Burkova T
Some morphological changes in the lungs after
experimental poisoning with Gramoxone.
Khig Zdraveopaz 16 ; 165-71 : 1973 (Russian)

Bulter C
Modification of paraquat inquiry in hamsters
Lab Invest 28 ; 379 : 1973

Conso F, Guillam C & Bescol-Liversac J
Poisoning by Dimethyl dipyridilium (Paraquat): Comment on
Images observed under the Electron Microscope.
Med Leg et Dommage Corp 6 ; 420-22 : 1973

Cooke NJ, Flenley DC & Matthew H
A Paraquat Poisoning: Serial Studies of Lung Function.
Qu Jl Med 42 ; 683-692 : 1973

de Lavour E, Grolleau G & Siou G
Experimental Poisoning of Hares by Paraquat-treated Alfalfa.
Ann Zool-Ecol Anim 5 ; 609-622 : 1973

Demidenko NM & Vengerskaya Kh Ya
Hygienic and Toxicological Characteristics of a New
Bipyridyl Phosphate Dessicant.
Med ZH Uzb 4 ; 9-10 : 1973 (Russian)

Douglas JF, McGeown MG & McEvoy J
The Treatment of Paraquat Poisoning: Three Cases of
Recovery.
Ulster med J 42 ; 209-12 : 1973

• 1973 (Cont)

Eliahou HE, Almog Ch, Gura V & Iaina A
 Treatment of Paraquat Poisoning by Haemodialysis.
Israel J Med Sci 9; 459-462 : 1973

Farrington JA, Ebert M, Land EJ & Fletcher K
 Bipyridilium Quaternary Salts and Related Compounds.
 V. Pulse Radiolysis Studies on the Reaction of Paraquat
 Radical with Oxygen, Implications for the Mode of Action
 of Bipyridilium Herbicides.
Biochim biophys Acta 314; 372-381 : 1973

Faure J, Marka C, Faure H, Yacub M & Cau G
 Histopathological and Toxicological Details of Fatal
 Paraquat Poisoning.
Med Leg et Dommage Corp 6; 417-19 : 1973

Fisher HK, Clements JA & Wright RR
 Pulmonary Effects of the Herbicide Paraquat studied 3 days
 after injection in Rats
J appl Physiol 35; 268-273 : 1973

Fisher HK, Clements JA & Wright RR
 Enhancement of Oxygen Toxicity by the Herbicide Paraquat.
Am Rev resp Dis 107; 246-252 : 1973

Fujita K
 Chemical Burns on the Cornea caused by 'Gramoxone' Weedkiller.
Nihon Noson Igakkai Zasshi 22; 194-5 : 1973 (Japan)

Fujita K
 Ocular Chemical Burns by a Herbicide, Paraquat Dichloride.
 (Rinsho Ganka) 27; 1399-1401: 1973 (Japan)
Pestic Abstr 7; 1896 : 1974

Gardiner TH, Schanker LS
 Effect of Paraquat-induced lung damage on
 permeability of rat lung to drugs.
Fed Proc 32; 748 : 1973

Gaultier M, Bescol-Liversac J, Frejaville JP, Leclerc JP &
 Guillam C.
 Anatomo-clinical and Experimental Studies of Intoxication by
 Paraquat.
Sem Hop Paris 49; 1972-1987: 1973

Jones GR & Owen-Lloyd P
 Recovery from Poisoning by 20% Paraquat.
Br J clin Pract 27; 69-70 : 1973

Kimbrough RD
 Paraquat Poisoning
J Am med Ass 223; 692-3 : 1973

• 1973 (Cont)

Kimbrough RD & Linder RE

The Ultrastructure of the Paraquat Lung Lesion in the Rat.
Environ Res 6; 265-273: 1973

Kodagoda N, Jayewardene RP & Attygalle D
 Poisoning with Paraquat: Case Report.
Forensic Sci 2; 107-111: 1973

Kopaczyk-Locke K

Effects of Paraquat and Diquat on Rat Liver Mitochondria.
Fed Proc 32; 250: 1973

Krieger RI, Lee PW, Black A & Fukuto TR

Inhibition of Microsomal Aldrin Epoxidation by Diquat and
 Several Related Bipyridylum Compounds.

Bull environ Contam & Tox 9; 1-3: 1973

Litchfield MH, Daniel JW & Longshaw S

The Tissue Distribution of the Bipyridylum Herbicides, Diquat
 and Paraquat in Rats and Mice.

Toxicology 1; 155-165: 1973

Malmqvist E, Grossman G, Ivemark B, & Robertson B

Pulmonary Phospholipids and Surface Properties of Alveolar
 Wash in Experimental Paraquat Poisoning.

Scand J resp Dis 54; 206-214: 1973

Moriyama I, Ide H, Ichikawa H & Hikosaka R

A Death by Acute Pulmonary Fibrosis after swallowing Gramoxone
 by Mistake.

(Nippon-kyobu-Shukkan Gakkai Zasshi (Jap J Thorac Dis) 11 (5)
 316 1973) (Japan)

Hlth Asp Pest 6; 73-2635: 1973

Muscarella A & Galofaro V

Pathological Lesions in some Fresh-water Fish caused by Paraquat.

(Nuova Vet 49; 211-221: 1973) (Italian)

Vet Bull 44; 3330: 1974

Nakamura I, Maeda M, Mori M, Miki S, Teranishi Y.

A case of Intoxication due to Paraquat Dichloride

(Nippon Naika Gakkai Zasshi 62 (10); 1394: 1973) (Japan)

Pestic Abstr 7; 74-1122: 1974

Neoral L, Kosatik A, Smysl B, Kubista P & Nemcova O

A Contribution to the Toxicological Demonstration, Pathogenesis
 and Time Relation of Changes following Acute Gramoxone (Paraquat)
 Poisoning. Part 1. Toxicological Demonstration of Poisoning.

Cesk Patol 9; 1-5: 1973 (Czech)

Neoral L, Kosatik A, Smysl B, Kubista P & Nemcova O

A Contribution to the Toxicological Demonstration, Pathogenesis
 and Time Relation of Changes following Acute Gramoxone (Paraquat)
 Positioning. Part II. Pathogenesis and Time Dependence of Organ
 Changes.

Cesk Patol 9; 49-58: 1973 (Czech)

• 1973 (Cont)

Rivera M

Diagnosis of Geese Poisoning with Gramoxone.

(Rev Cubana Farm 7 (1); 65-70:1973) (Spanish)

Chem Abstr 81; 164312: 1974

Robertson B

Paraquat Poisoning as an Experimental Model of the

Idiopathic Respiratory Distress Syndrome.

Bull Physio-path res 9; 1433-1452: 1973

Rogers PAM, Spillane TA, Fenlon M & Henaghan T.

Suspected Paraquat Poisoning in Pigs and Dogs.

Vet Rec 93; 44-45: 1973

Sinow J & Wei E

Ocular Toxicity of Paraquat

Bull environ Contam & Tox 9; 163-168: 1973

Slocombe G, Thorn PE, Toohill J & Wood J

A Case of Paraquat Poisoning

Nursing Times 66 111-2 1973

Smalley HE

Toxicity and Hazard of the Herbicide, Paraquat, in Turkeys

Poult Sci 52; 1625-8: 1973

Staiff DC, Irle GK & Felenstein WC

Screening of Various Adsorbents for Protection against Paraquat

Poisoning

Bull env contam & Toxicol 10; 193-99: 1973

• 1974

Anon

The Paraquat Puzzle

Med J Aust 2; 800-1: 1974

Almog C & Siegelbaum Y

Paraquat Poisoning in Israel

Harefuzah 87; 400-3: 1974 (Hebrew)

Autor AP

Reduction of Paraquat Toxicity by Superoxid Dismutase

Life Sci 14; 1309-1319: 1974

Bainova A, Antor G

Enzyme studies on lung homogenates after intoxication

with Gramoxone

Khig Zdraveopaz 17; 329-36: 1974

Baran RL

Nail Damage caused by Weedkillers and Insecticides

Archs Derm 110; 467: 1974

• 1974 (Cont)

Bedwell W & Anderson WH
Paraquat and Oxygen Effects on Surfactants.
Clin Res 22; 44A : 1974

Borchard F
Ultrastructural and Light Microscopical Findings in 3 cases of
Paraquat Poisoning with Prolonged Lethal course.
Pneumonologie 150; 185-189: 1974 (French)

Borchard F, Grabensee B, Jax W and Huth F
Morphological Findings in Cases of Paraquat Poisoning.
Klin Wschr 52; 657-671: 1974 (German)

Brown EAB
The Localisation, Metabolism and Effects of Drugs and Toxicants
in Lung. Paraquat and Related Dipyridyls.
Drug Metabolism Reviews 3; 33-87: 1974

Bus JS, Aust SD & Gibson JE
Superoxide and Singlet Oxygen-catalysed Lipid Peroxidation
as a possible Mechanism for Paraquat (methyl viologen) Toxicity.
Biochem biophys Res Commun 58; 749-755: 1974

Copland GM, Kolin A & Shulman HS
Fatal Pulmonary Intra-alveolar Fibrosis after Paraquat Ingestion.
New Engl J Med 291; 290-2 : 1974

Davies DS, Davies DL
Effect of d-propanolol and superoxide dismutase on paraquat
reduction and adreno chrome formation by rat liver microsomes.
Fed Proc 33; 228: 1974

Dobbelaere F, Bouffioux J
Leukonychia in bands due to Paraquat.
Arch Belg Dermatol 30; 283-4 : 1974

Douze JMC, van Dijk A, Gimbrere JSF, van Heijst ANP, Maes R &
Rauws AG
Intensive Therapy after Paraquat Intoxication.
Intensivmedizin 11; 241-50: 1974 (Dutch)

Fletcher K
Paraquat Poisoning, In: Forensic Toxicology p 86-98
Ed. B. Ballantyne Publ John Wright & Sons Ltd 1974

Grabensee B
Clinical Treatment of Paraquat Intoxication.
Pneumonologie 150; 173-9: 1974

• 1974 (Cont)

Guyon F, Bismuth C, Leclerc J-P & Dauchy F
 Massive Poisoning with Paraquat Death in less than 24 hours.
 Toxicological and Anatamoclinical Data.
Eur J Toxicol environ Hyg 7; 182-187: 1974

Ilett KF, Stripp B, Menard RH, Reid ND & Gillette JR
 Studies on the Mechanism of the Lung Toxicity of Paraquat:
 Comparison of Tissue Distribution and some Biochemical Parameters
 in Rats and Rabbits.
Toxic appl Pharmac 28; 216-226: 1974

Kacew S & Witschi H
 Acute Paraquat Poisoning: Influence on Selected Pulmonary
 Enzymes.
Pharmacologist 16; 299: 1974

Kimbrough RD
 Toxic Effects of the Herbicide Paraquat.
Chest 65 (suppl); 65-67: 1974

Kimura M, Kameda T, Suzuki Y, Sugaya T, Kurokawa S, Hayashi S
 Studies on Skin Patch Tests for contact Dermatitis by Pesticides
(Ann Rep Akita Inst Rural Med 4; 77-80: 1974) (Japan)
Pest Abstr 10; 77-2366: 1977

Kohegyi I, Gogl A, Farkas GY, Mezey B
 Poisonings caused by dipyridyl herbicides
 Gramoxone, Gamex, Reglone
Medicus Universalis VII (4); 199-201: 1974 (Hungarian)

Kusic R et al
 Clinical and histopathological study on paraquat poisoning
Vojnosanit Pregl 31; 397-9: 1974 (Yugoslav)

Lareng L, Fabre J & Cathala B
 Paraquat fatal intoxications
Nouv Presse med 4; 930: 1974 (French)

Lautenschläger JB
 Isolated aplastic anaemia after paraquat poisoning
Blut 28; 221: 1974 (German)

Lautenschläger J, Grabensee B & Pöttgen W
 Paraquat Poisoning and Isolated Aplastic Anaemia.
Dtsch med Wschr 99; 2348-2351: 1974 (German)

Lewis TD
 Paraquat Overdose.
Med J Aust 2; 814-5: 1974

Luts-Ostertag Y & Henou Ch
 The Action of Paraquat on the Urogenital Tract of the Embryo
 of Hen and Duck.
CR Seances Soc Biol, Clermont-Ferrand 168; 304-7: 1974 (French)

- 1974 (Cont)

Maling HM, Saul W, Williams MA, Brown EA, Gillette JR
 The relation of the potentiation of paraquat 48-hour mortality in rats and mice by l-isoproterenol to its effects on renal clearance of paraquat
Pharmacologist 18; 244: 1974

McCaughey H
 Paraquat Overdose
Med J Aust 2; 855-6: 1974

Milhaud G
 Toxicity of Paraquat- question and answer
Recueil Med Veterinaire 150; 337: 1974 (French)

Murray RE & Gibson JE
 Paraquat Disposition in Rats, Guinea-pigs and Monkeys.
Toxic appl Pharmac 27; 283-291: 1974

Ongom VL, Owor R & Tonuisange ET
 Paraquat (Gramoxone) used as a pediculocide
 In: The Use and Abuse of Drugs and Chemicals in Tropical Africa. Ed Bagshawe AF et al.
 Nairobi, East Afr Lit Bureau. 1974. 229-233

Pariente R, Bismuth Ch, Legrand M, Gauthier M
 Data provided by Ultra-structural Study in Two Cases of Paraquat Poisoning in Man.
Rev Franc Malad Resp 2; 968-77: 1974 (French)

Pasi A, Embree JW, Eisenlord GH & Hine CH
 Assessment of the Mutagenic Properties of Diquat and Paraquat in the Murine Dominant Lethal Test.
Mutat Res 26; 171-5: 1974

Poche R
 The Pathology of the Paraquat Lung
Pneumonologie 150; 181-4: 1974 (French)

Ramachandran S, Rajapakse CNA & Perera MVF
 Further Observations on Paraquat Poisoning in Man.
Forensic Sci 4; 257-66: 1974

Restuccia A, Foglini A, De Alentis Nannini D
 Paraquat Toxicity for rabbits
Vet Ital 25; 555-565: 1974 (Italian)

Rhodes ML
 Hypoxic Protection of Paraquat Poisoning
 A Model for respiratory distress syndrome
Chest 63 (3) Abstr 341-2 1974

Rose MS, Crabtree HC, Fletcher K & Wyatt I
 Biochemical Effects of Diquat and Paraquat: Disturbance of the Control of Corticosteroid Synthesis in Rat Adrenal and Subsequent Effects on the Control of Liver Glycogen Utilization
Biochem J 138; 437-443: 1974

• 1974 (Cont)

Rose MS, Smith LL & Wyatt I
 Evidence for the Energy-dependant Accumulation of Paraquat
 into Rat Lung.
Nature 252; 314-5: 1974

Roujeau J, Nogues CR & Leclerc JP
 Paraquat Poisoning: Pathology and Clinical and Experimental
 Study.
Rev Fr Mal Resp 2; 65-74: 1974 (French)

Siebert D & Lemperle E
 Genetic Effects of Herbicides: Induction of Mitotic Gene
 Conversion in *Saccharomyces cerevisiae*.
Mutat Res 22; 111-120: 1974

Smith LL, Wright A, Wyatt I & Rose MS
 Effective Treatment for Paraquat Poisoning in Rats and its
 Relevance to the Treatment of Paraquat Poisoning in Man.
Br Med J 4; 569-71: 1974

Smith P & Heath D
 The Ultrastructure and Time Sequence of the Early Stages
 of Paraquat Lung in Rats.
J Path 114; 177-184: 1974

Smith P & Heath D
 Paraquat Lung: A reappraisal
Thorax 29; 643-53: 1974

Smith P, Heath D & Kay JM
 The Pathogenesis and Structure of Paraquat-induced
 Pulmonary Fibrosis in Rats.
J Path 114; 57-67: 1974

Styles JA
 Studies on the Effects of Paraquat and Diquat on Cells
 in Culture: Viability of Macrophages and Fibroblasts
 incubated with Paraquat and Diquat.
Br J exp Path 55; 71-77: 1974

Von Eisenmenger V, Henn R, Beckman G
 Clinical and Pathological aspects of Paraquat Poisoning
Beitr Gerichte Med 32; 262-6: 1974 (German)

Witschi HP & Kacew S
 Studies on the Pathological Biochemistry of Lung Parenchyma
 in Acute Paraquat Poisoning.
Med Biol 52; 104-110: 1974

Yamashita K, Aoyama S, Ikuta S, Miyake T & Arima K.
 A Case of Acute Intoxication and Autopsy, due to Paraquat
 Dichloride: Comment on Comparison between the Injury by
 Insecticide and Herbicide.
(Nippon Noson Igakkai Zasshi 23 (1); 27-38: 1974) (Japan)
Pestic Abstr 7; 1888: 1974

• 1975

Alary MMJ, Vergnes JL, Coeur A, Cantin D
 Bipyridinium derived herbicide residues in foods
 Physicochemical and toxicological study
Bull Treu Soc Pharm Lyon 18; 131-7 : 1975 (French)

Baldwin RC, Pasi A, MacGregor JT & Hinc CH
 The Rates of Radical Formation from the Dipyridylium Herbicides,
 Paraquat, Diquat and Morfamquat in Homogenates of Rat Lung.
 Kidney and Liver: An Inhibitory Effect of Carbon Monoxide.
Toxic appl Pharmac 32; 298-304 : 1975

Baynova A
 Cumulative Action of Gramoxone and Reglone
Prcbl Khig 1; 31-8 : 1975 (Russian)

Bescol-Liversac J, Paquelin A & Guillam C
 An ultrastructural study of a renal biopsy of a
 patient poisoned by paraquat.
Eur J Toxicol 8; 236-46 : 1975

Binnie GAC
 Paraquat
Lancet I; 169-70 : 1975

Brown EAB & Maling HM
 The Effects of Paraquat and related Herbicides on the Acetylcholinesterase
 of Rat Lung.
Fed Proc Fed Am Soc exp Biol 34; 226 : 1975

Brown EAB & Maling HM
 Effects of propanolol and paraquat on incorporation
 of ³²p-phosphate into phospholipids of rat lung slices
Pharmacologist 17; 203 : 1975

Bus JS
 Paraquat perinatal toxicity and a proposed mechanism
 of action involving lipid peroxidation
(Diss Abstr Int B 36; 2748 : 1975)
Pest Abstr 9; 726 : 1976

Bus JS, Aust SD & Gibson JE
 Lipid Peroxidation: A possible Mechanism for Paraquat Toxicity.
Res Commun Chem Path Pharm 11; 31-38 : 1975

Bus JS & Gibson JE
 Postnatal toxicity of chronically administered paraquat
 in mice and interactions with oxygen and bromobenzene
Toxic appl Pharmac 33; 461-70 : 1975

Bus JS, Preache MM, Cagen SZ, Posner HS, Eliason BC,
 Sharp CW & Gibson JE
 Fetal toxicity and distribution of paraquat and diquat
 in mice and rats.
Toxic appl Pharmac 33; 450-60 : 1975

• 1975 (Cont)

Butler C

Pulmonary interstitial fibrosis from paraquat
in the hamster

Arch Path 99; 503-7: 1975

Carson DJL & Carson ED

The increasing use of paraquat as a suicidal agent
Forens Sci 5; 114: 1975.

Cegla UH, Kroidl RF, Kronberger H & Weber H

Experimental Model of Lung Fibrosis in the Rat
using Paraquat Injections
Pneumonologie 152; 65-74: 1975 (French)

Conolly ME

Paraquat Poisoning - Clinical Features.

Proc roy Soc Med 68; 441:1975

Cooper P

Paraquat revisited

BIBRA Inf Bull 14 (8); 387-90: 1975

Corrin B, Vijeyaratnum GS

Experimental models of interstitial pneumonia : Paraquat, Iprindole
Prog Resp Dis 8; 107-120: 1975

Davies DS, Conolly ME

Paraquat Poisoning - Possible therapeutic approach
In: Lung Metabolism. Ed Junod AF. New York,

Academic Press, 1975. 275-277

Davies DS & Conolly ME

Paraquat Poisoning - Possible Therapeutic Approach

Proc roy Soc Med 68; 442: 1975

Davies RE

The Paraquat Puzzle

Med J Aust 1; 45: 1975

Ecker JL, Gibson JE & Hook JB

In Vitro analysis of the renal handling of Paraquat
Toxic appl Pharmac 34; 170-77: 1975

Ecker JL, Hook JB & Gibson JE

Nephrotoxicity of Paraquat in Mice

Toxic appl Pharmac 34; 178-86: 1975

Fairshter RD & Wilson AF

Paraquat Poisoning : Manifestations and Therapy

Am J Med 59; 751-753: 1975

Fawell JK

Applications of quantitative morphology in toxicology

Proc Eur Soc Tox 16; 285-9: 1975

• 1975 (Cont)

Fisher HK, Clements JA, Tierney DF & Wright RR
Pulmonary Effects of Paraquat in the First Day after Injection
Am J Physiol 228; 1217-1223: 1975

Fletcher K
Paraquat
Lancet I; 278: 1975

Fridovich I
A Free radical pathology: Superoxide radical and superoxide
dismutases
Ann Rep Med Chem 10; 257- 264: 1975

Gervais P, Diamant-Berger O, Bescol-Liversac J, Guillam C & Guyon F
Forensic and Medico-social Problems of Acute Intoxications by
Herbicides of Paraquat Group
Archs Mal Prof 36; 19-36: 1975

Hancock BW, Martin JF, Ward JF, Kilpatrick R
Attempted suicide with a pesticide mixture
Resuscitation 4; 265-9: 1975

Jaques M, Decoster J, Archichvili D, Martens M
Recent case of Paraquat poisoning. Early elimination of the
poisoning by forced diuresis and by haemodialysis
Rev Tossicol Sper Sper Clin 5; 361-6: 1975 (Italian)

Laithwaite JA
Paraquat Poisoning treated with Immunosuppressants and
Potassium Aminobenzoate.
Br med J 1; 266-7: 1975

Larebng L, Fabre B, Cathala B, Fabre-Planques M, Voigt J-J & Counillon F
Fatal Paraquat Poisonings.
Concours Med 97; 680-7: 1975 (French)

Lutz-Ostertag Y & Henon C
Teratology. Paraquat: Embryo mortality and effects
on the pulmonary apparatus of the chicken and quail embryos.
CR Acad Sc Paris 281 Series D; 439-442: 1975 (French)

Maini R & Winchester JF
Removal of Paraquat from Blood by Haemoperfusion over
Sorbent Materials.
Br Med J 3; 281-2: 1975

Malcolmson E & Beesley J
Unsuccessful Immunosuppressant Treatment of Paraquat Poisoning.
Br med J 3; 650-651: 1975

Maling HM et al
Propanolol Treatment of Experimental Paraquat Poisoning
in Rats.
Fed Proc Fed Am Soc exp Biol 34; 226: 1975

• 1975 (Cont)

Montgomery MR
 Interaction of Paraquat with Fatty Acid Desaturase activity in Rat Lung Microsomes.
Pharmacologist 17; 203:1975

Nakabayashi H, Yasuga N, Hara I, Shimizu F
 Two cases of poisoning by the herbicide Gramoxone:
 An occupational case in a 59 year old male and a case of suicide in a 24 year old woman.
Sangyo Igaku 17; 53: 1975 (Japan)

Okonek S, Hofmann A
 Clinical and toxicological investigations on the elimination of diquat by extracorporeal haemodialysis
Verh Dtsch Ges Inn Med 81; 699-701: 1975 (German)

Okubo S, Kanezawa Y, Tachikawa H, Nayashi S
 Komatsuda H, Hirata T, Watanuki T
 Findings in two autopsies performed after fatal paraquat dichloride poisoning.
(Nippon Noson Igakkai Zasshi 24; 460-1: 1975) (Japan)
Pest Abstr 9; 409: 1976

Okura K, Tsutsui S, Suzuki M
 Nakanishi M & Nakabayashi H
 A study of the toxicity of Paraquat
Nihon Noson Igakkai Zasshi 24; 458-59: 1975 (Japan)

Pasi A & Embree JW
 Further Comments on the Assessment of the Mutagenic Properties of Diquat and Paraquat in the Murine Dominant Lethal Test.
Mutat Res 31; 127-128: 1975

Plotnick HB
 Studies of the mechanism of paraquat toxicity
Diss Abstr Int B 35; 4078-9: 1975

Roujeau J, Leclerc JP
 Mechanism of action of Bleomycin and Paraquat in the genesis of interstitial pneumoconiosis
Prog Resp Dis 8; 121-2: 1975

Smith P & Heath D
 The Pathology of the Lung in Paraquat Poisoning
J Clin Path 28 (Suppl 9) 81-93: 1975

Staiff DC, Comer SW, Armstrong JF & Wolfe HR
 Exposure to the herbicide Paraquat
Bull environ contamin & Toxicol 14; 334-40: 1975

Tsunenari S, Muto H, Inoue S, Sasaki S, Sugita H & Kanda M
 Forensic Toxicological Studies of the herbicide Gramoxone
Nippon Hoigaku Zasshi 29 (2); 88-102: 1975 (Japan)

• 1975 (Cont)

Van Dijk A, Maes RAA, Drost RH, Douze JMC & Van Heyst ANP
 Paraquat Poisoning in Man
Arch Toxicol 34; 129-136: 1975

Van Osten GK & Gibson JE
 Effect of Paraquat on the Biosynthesis of Deoxyribonucleic Acid, Ribonucleic Acid and Protein in the Rat.
Food Cosmet Toxicol 13; 47-54: 1975

Varga T, Szabo A, Rakoczy I
 A Case of Fatal Paraquat Poisoning
Morph Igasag Orv Szemle 15; 142-148: 1975 (Hungarian)

Verne J, Fournier Et, Hebert S & Richshoffer N
 The action of a herbicide (paraquat) on hepatocytes
 in histiotypic culture
Eur J Toxicol 8; 226-228: 1975

Vizek M, Holusa R & Palacek F
 Lung function in acute paraquat intoxication
Physiol bohemoslov 24; 559-563: 1975 (Czech)

Widdop B, Medd RK, Braithwaite RA, Vale JA
 Haemoperfusion in the treatment of Paraquat poisoning
Proc Europ Soc Artific Organs 2; 244-7: 1975

Wills A
 Paraquat Poisoning
NZ med J 81; 357: 1975

• 1976

Anon
 Paraquat Poisoning
Lancet I; 1057: 1976

Abrams RM, Notelovitz M, Wilcox CJ
 Stimulation of the pentose cycle by paraquat in isolated perfused rat lung.
Physiologist 19 (3); 117: 1976

Anderson D, McGregor DB & Purchase IFH
 Dominant Lethal Studies with paraquat and diquat in male CD-1 mice.
Mutat Res 40; 349-58: 1976

Barraclough BM
 Paraquat Poisoning
Lancet 1; 1353: 1976

Bassett DJP, Fisher AB
 Stimulation of the pentose cycle by paraquat in isolated perfused rat lungs
The Physiologist 19; 117: 1976

• 1976 (Cont)

Bennett PN, Davies DS & Hawkesworth GM
In vitro absorption studies with paraquat and diquat
in the dog.
Br J Pharmacol 58; 284P : 1976

Binns CW
A deadly cure for lice - A case of paraquat poisoning.
Papua N Guinea med J 19; 105-7 : 1976

Bus JS, Cagen SZ, Olgaard M & Gibson JE
A mechanism of paraquat toxicity in mice and rats
Toxic appl Pharmac 35; 501-513 : 1976

Bus JS, Aust SD, Gibson JE
Paraquat toxicity: Proposed Mechanism of action involving
lipid peroxidation.
Environ Hlth Perspect 16; 139-46 : 1976

Cagen SZ, Janoff AS, Bus JS, Gibson JE
Effect of paraquat (methyl viologen) on the liver function
in mice.
J Pharm exp Ther 198; 222-228 : 1976

Carson DJL, Carson ED
The increasing use of paraquat as a suicide agent
Forens Sci 7; 151-60 : 1976

Cretney MJ
A child paraquat death
Bull Int Ass Forens Toxicol 12 (3); 11 : 1976

Dally S
Paraquat Poisoning Risk
Lancet II; 689: 1976

Davies RE
The Paraquat Puzzle
Med J Aust 1; 278-280: 1976

Davies RE
The management of paraquat poisoning
NZ med J 83; 244-5 : 1976

Fairshiter RD, Rosen SM, Smith WR, Glasser FL, McRae DM
& Wilson AF
Paraquat Poisoning : New aspects of Therapy
Quart J Med 45; 551-565 : 1976

Fisher UK
Paraquat disturbs metabolism of dipalmitoyl
phosphatidylcholine in lungs of intact rats.
Clin Res 24; 159A : 1976

• 1976 (Cont)

Funke K, Gohler G, Futh U, Lignitz E
Clinical features, treatment and morphology of paraquat poisoning.
Dtsch Gesundheitsw 31; 2143-5: 1976 (German)

Gardiner TH & Schanker LS
Effect of paraquat-induced lung damage on permeability
of rat lung to drugs.
Proc Soc exp Biol Med 151; 288-292: 1976

Goulding R, Volans GN, Crome P & Widdop B
Paraquat Poisoning
Br Med J 1; 42:1976

Halliwell B
Ascorbic acid and paraquat toxicity
Lancet II; 854: 1976

Hubert JP, Janssen F, Smets R
Diffuse interstitial pneumopathy caused by paraquat poisoning
BRUX Med 5; 185-191: 1976 (French)

Janssen F, Baran D, Dubois J
Paraquat Poisoning in a child
Acta Paediatr Belg 29; 189-92: 1976 (French)

Johnson RP, Huxtable CR
Paraquat Poisoning in a dog and cat
Vet Record 98; 189-191: 1976

Khurana M, Niden AH
Experimental model to study the development of pulmonary fibrosis
Am Rev Resp Dis 113; 245: 1976

Konno J, Hongu M, Oizumi K, Arimichi F, Hayashi I
Experimental pulmonary fibrosis of rats
Nippon Naika Gakkai Zasshi 65; 602-3: 1976 (Japan)

Kratinsson J Johannesson T
Paraquat Suicide
Bull Int Ass Forens Toxicol 12 (3); 11-12: 1976

Laithwaite JA
Paraquat Poisoning
Br J Clin Pract 30; 71-73: 1976

Laws GJ
A case of paraquat poisoning
J Clin Path 29; 83: 1976

Leon Pacher RJ
Herbicide poisoning in a dog
Mod Vet Pract 57; 375: 1976

• 1976 (Cont)

Lloyd ELL
 Ascorbic Acid and paraquat toxicity
Lancet II ; 1255 : 1976

Lock EA, Smith LL & Rose MS
 Inhibition of paraquat accumulation in rat lung
 slices by a component of rat plasma and a variety
 of drugs and endogenous amines
Biochem Pharmac 25 ; 1769-1772 : 1976

Maling HM, Saul W, Williams MA, Brown EA, Gillette JR
 The relation of the potentiation of paraquat 48-hour mortality in
 rats and mice by l-isoproterenol to its effects on renal clearance
 of paraquat
Pharmacologist 18 ; 244 : 1976

Martin-Lalande J, Saint-Ruf G, Fraquet A, Gervais P
 Lung Fibrosis with an acute evolution, due to a slight
 and accidental ingestion of herbicide (of paraquat kind);
 dealing with a non-lethal case.
Revue Franc Malad Resp 4 ; 456-8 : 1976 (French)

McCormack J
 Paraquat Poisoning : Report of a survivor
J Irish Med Ass 69 ; 435-438 : 1976

Mikuni I Suzuki A
 A case of ocular corrosion by a herbicide paraquat dichloride
 (Ganka Rinsho Iho 70 ; 395-8 : 1976) (Japan)
Pest Abstr 9 ; 76-1933 : 1976

Mikuni I Suzuki A
 A case report of ocular erosion by paraquat dichloride
 (Kanagawa Igakukai Zasshi 3 (2) ; 76 : 1976) (Japan)
Pest Abstr 9 ; 76-2952 : 1976

Montgomery MR
 Interaction of Paraquat with the pulmonary microsomal
 fatty acid desaturase system
Toxic appl Pharmac 36 ; 543-554 : 1976

Montgomery MR
 Interaction of paraquat with pulmonary microsomal enzyme systems.
Toxic appl Pharmac 37 ; 106-7 : 1976

Niden AH & Khurana MML
 An animal model for diffuse interstitial pulmonary
 fibrosis - chronic low dose paraquat ingestion
Fed Proc 35 ; 2340 : 1976

• 1976 (Cont)

Okeneck S

Poisoning by paraquat or diquat
Med Welt 27; 1401-4: 1976 (German)

Okonek S, Hofmann A & Henningsen B

Efficacy of gut lavage, haemodialysis and
 haemoperfusion in the therapy of paraquat or diquat
 intoxication

Arch Toxicol 36; 43-51: 1976

Okeneck S, Hofmann S, Henningsen A

New possibilities for the treatment of cases of paraquat or diquat
 poisoning : Intestinal lavage and haemoperfusion.

Ver Deutsch Gesell Inn Med 82; 1954-8: 1976 (German)

Oskarsson A & Tjalive H

High uptake in the erythrocytes and the spleen of the
 quaternary dipyridylium salt paraquat injected intravenously
 in hypotonic solutions

Acta Pharma Tox 39; 481-99: 1976

Reddy Km Omaye S, Chin M, Litov R, Hasegawa G &
 Cross C

Effect of aspirin (ASA), indomethacin (IND) and hydrocortisone
 (HYC) pretreatments on selected aspects of rat lung metabolism
 before and after paraquat administration

Am Rev Resp Dis 113; 102: 1976

Reddy K, Omaye S, Chin M, Litov G, Hasegawa G & Cross C
 Biochemical effects of antiinflammatory agents on the
 survival of rats in acute paraquat toxicity.

Fed Proc 35; 1656: 1976

Reeve J & Cox AG

Paraquat Poisoning

Lancet 1; 1247: 1976

Rhodes ML, Zavala DC & Brown D

Hypoxic protection in paraquat poisoning

Lab Invest 5; 496-500: 1976

Robertson B, Grossman G & Ivemark B

The alveolar lining layer in experimental paraquat poisoning.

Acta Path Microbiol Scand Sect A 84; 40-46: 1976

Rose MS, Lock EA, Smith LL & Wyatt I

Paraquat accumulation. Tissue and species specificity

Biochem Pharmac 25; 419-423: 1976

Rose MS, Smith LL & Wyatt I

The relevance of pentose phosphate pathway stimulation in
 rat lung to the mechanism of paraquat toxicity

Biochem Pharmac 25; 1763-1767: 1976

- 1976 (Cont)

Schlatter I
 Paraquat Poisoning
Schweiz Runds Med 65; 837-843: 1976

Schwartz LW & Silverman S
 Paraquat induced pulmonary damage in non-human
 primates: A morphological study
Am Rev Resp Dis 113; 108: 1976

Simons RS, Jackett PS, Carroll MEW & Lowrie DB
 Superoxide independence of paraquat toxicity in
Escherichia coli
Toxic appl Pharmac 37; 271-280: 1976

Smith P, Heath D
 Paraquat (Review article)
CRC Crit Rev Toxicol 4; 411-445: 1976

Smith LL, Lock EA, Rose MS
 The relationship between 5-hydroxytryptamine
 and paraquat accumulation into rat lung
Biochem Pharmacol 25; 2485-7: 1976

Sugimoto T
 The occurrence of ocular lesions due to paraquat
 dichloride and their alleviation
Sangyo Igaku 18; (3): 222-3 1976 (Japan)
Pest Abstr 10; 77-0169: 1977

Suzuki H Tsutsui J, Nakamura Y, Ito Y, Kato H, Nakabayashi H
 Studies on toxicity of paraquat dichloride Part 2:
 The effectiveness of CDP-choline and superoxide dismutase for
 treatment
(Nippon Noson Iggakai Zasshi 25; 336-7: 1976) (Japan)
Pest Abstr 9; 76-3031: 1976

Teare RD
 Poisoning by Paraquat
Med Sci Law 16; 9-12: 1976

Teare D & Brown S
 Poisoning by paraquat.
Med leg J 44; 33-47: 1976

Tsunenari S, Kita G, Obo S, Ogata Y
 A toxicological study of Gramoxone weedkiller
 of relevance to forensic medicine
Nippon Hogaku Zasshi 29; 236-7: 1976 (Japan)

Ward CD, Stones DPA, Connell H, Cullen DR, Watkin JL
 Paraquat poisoning
Lancet 1; 1247: 1976

- 1977

Autor A P, Schmitt SI
 Pulmonary fibrosis and paraquat toxicity
 In: Biochemical Mechanisms of Paraquat Toxicity.
 (ed Autor AP), New York, Academic Press. 1977. 175-186.

Bainova A, Vulcheva V
 Lung changes after chronic paraquat intoxication
Dokl Bolg Akad Nauk 30; 1788-1790 : 1977 (Bulgarian)

Block ER, Wasserman B, Rostand R, Hood CI
 Prevention of acute paraquat toxicity in rats by
 superoxide dismutase (SOD)
Am Rev Resp Dis 115; 306 : 1977

Bouletreau P, Ducluzeau R, Bui-Xuan B, Petit P, Motin J
 Acute renal complications of acute intoxications
Acta Pharmac Tox 41; Suppl II 49-63 : 1977

Boye GL, Huang CT, Michelakis AM
 The effect of paraquat on rat lung cyclic nucleotides
Pharmacologist 19; 117 ; 1977

Bus JS, Aust SD, Gibson JE
 Lipid peroxidation as a proposed mechanism for paraquat
 toxicity
 In: Biochemical Mechanisms of Paraquat Toxicity.
 (ed Autor AP) New York, Academic Press. 1977. 157-174

Cagen SZ, Gibson JE
 Liver damage following paraquat in selenium deficient and
 diethyl maleate pretreated mice
Toxicol Appl Pharmacol 40; 193-200: 1977

Cavalli RD, Fletcher K
 An effective treatment for paraquat poisoning
 In: Biochemical Mechanisms of Paraquat Toxicity
 (ed Autor AP) New York, Academic Press. 1977. 213-230

Conolly ME, Davies DS, Draffen GH, Bennett PN, Dollery CT
 Clinical experience with paraquat poisoning
 In: Clinical Aspects of Paraquat Poisoning (ed Fletcher K)
 London, ICI Ltd. 1977. 1- 11.

Cross CE, Reddy ICA, Hasegawa GK, Chiu MM, Tyler WS, Omaye ST
 Paraquat toxicity: effects of selenium deficiency and
 anti-inflammatory drug pretreatments
 IN: Biochemical Mechanisms of Paraquat Toxicity
 (ed Autor AP) New York, Academic Press. 1977. 201-212.

Darke PGG Gibbs C Kelly DF Morgan DG
 Pearson H Weaver BM
 Acute respiratory distress in the dog associated with paraquat poisoning.
Vet Record 100; 275-7 : 1977

Davies DS, Hawksworth GM, Bennett PN
 Paraquat Poisoning
Proc Europ Soc Toxicol 18; 21-6 : 1977

• 1977 (Cont)

Douze JMC, van Dijk A, Gimbrere JSF, van Heijst ANP, Maes RAA
 Intensive therapy after paraquat intoxication
 In: Clinical Aspects of Paraquat Intoxication (ed Fletcher K)
 London, ICI Ltd. 1977. 34-45.

Douze JMC, van Heijst ANP
 The paraquat intoxication - oxygen a real problem
Acta Pharmac Tox 41 : Suppl II · 241-5 ; 1977

Farr MJ
 Paraquat toxicity
Practitioner 219 ; 356-9 : 1977

Fisher HK
 Two experiments not previously described
 In: Clinical Aspects of Paraquat Poisoning (ed Fletcher K)
 London, ICI Ltd. 1977. 74-80.

Fisher HK
 Importance of oxygen and of pulmonary surfactant in lung
 injury of paraquat
 In: Biochemical Mechanisms of Paraquat Toxicity
 (ed Autor AP) New York, Academic Press. 1977. 57-69

Fitzgerald GR, Barniville G, Black J, Silke B, Carmody M, O'Dwyer WF
 Occupational paraquat poisoning
Quart J Med 46 ; 561-2 : 1977

Fitzgerald GR, Barniville G, Fitzpatrick P, Edwards A, Silk B
 Adrenal abnormalities in paraquat poisoning. An indication for
 corticosteroid therapy?
Irish J Med Sci 146 ; 421-3 : 1977

Fodre Z, Sipos K, Berencsi
 Study of the irritant and allergic effects of Gramoxone in guinea pigs
Egeszsegstudomany 21 ; 244-9 : 1977 (Hungarian)

Fungi L, Mora P, Cavallaro S, Mossetti G, Malvestio G
 A case of fatal herbicide poisoning
Minerva Paediatrician 29 ; 1525-32 : 1977

Gibson JE, Cagen SZ
 Paraquat induced functional changes in kidney and liver
 In: Biochemical Mechanisms of Paraquat Toxicity
 (ed Autor AP) New York, Academic Press. 1977. 117-136

Gimbrere J, Douze J, Gerritsen S
 Controlled hypoxic hypothermia in the treatment of paraquat
 poisoning
Intensive Care Med 3 ; 195; 1977

Grcevic N, Jadro-Santel D, Jukic S
 Cerebral changes in paraquat poisoning. In:
Neurotoxicology Vol I Ed Roisin L, Shiraki H & Grcevic N
 N.Y., Raven Press 1977. 469-484.

• 1977 (Cont)

Greenberg DB, Last JA

Collagen biosynthesis by lung slices from rats administered paraquat, a fibrotic agent

Chest 72 (3); 400 : 1977

Harley JB, Grinspan S, Root RK

Paraquat suicide in a young woman : Results of therapy directed against the superoxide radical

Yale J Biol Med 50 ; 481-488 : 1977

Hasegawa G & Gorin AB

Clearance of paraquat from plasma and lung lymph in sheep
Am Rev Resp Dis 115 (4); 220 : 1977

Hassan HM

Regulation of the synthesis of superoxide dismutase in Escherichia coli. Induction of methyl viologen
J Biol Chem 252 ; 7667-72 : 1977

Havill JH, Rothwell RPG, Chiu L, Leng RE, Wardill J

Accidental paraquat poisonings

N Z Med J 85 ; 512-4 : 1977

Heath D, Smith P

The pathology of the lung in paraquat poisoning

In: Biochemical Mechanisms of Paraquat Toxicity
(ed Autor AP) New York, Academic Press. 1977. 117-136

Hollinger MA Chvapil M

Effect of paraquat on lung propyl hydroxylase

Res Commun Chem Path Pharm 16 ; 159-62 : 1977

Hollinger MA, Giri SN, Freywald M

Effect of parenteral zinc on paraquat toxicity in the rat

Res Commun Chem Path Pharm 18 ; 689-696 : 1977

Hosli J

Paraquat poisoning in dogs

Schwarz Arch Tierheilkd 119 ; 377-381 ; 1977 (German)

Jones RW, Garland PB

Sites and specificity of the reaction of bipyridylium compounds with anaerobic respiratory enzymes of escherichia coli. Effects of permeability barriers imposed by the cytoplasmic membrane

Biochem J 164 ; 199-211 : 1977

Klaff IJ, Levin PJ, Potgieter PD, Losman JG, Nohomovitz LE Ferguson AD

Treatment of Paraquat poisoning with the membrane oxygenator
South Afr Med J 51 ; 203-7 : 1977

- 1977 (Cont)

Kopazyk - Locke K

In vitro and in vivo effects of paraquat on rat liver mitochondria

In: Biochemical Mechanisms of paraquat toxicity

(ed Autor AP) New York, Academic Press. 1977. 93-115.

Kuhara H, Wakabayashi T, Kishimoto H, Hayashi K, Suti T, Matsunga T
Five autopsy cases of paraquat poisoning

Nippon Noson Igakka Zasshi 26 : 647-656 ; 1977

Larsson B, Oskarsson A, Tjälve H

Binding of paraquat and diquat on melanin

Exp Eye Res 25 ; 353-61 : 1977

Ledwith A

Electron transfer reactions of paraquat. In:

Biochemical Mechanisms of Paraquat Toxicity

(ed Autor AP) New York. Academic Press. 1977. 21-38.

Mahieu P, Hassoun A, Fautsch G, Lauwerijs R and Tremouroux J
Paraquat poisoning. Survival without pulmonary insufficiency
after early bleomycin treatment

Acta Pharmacol 41 ; Supp II 246-8 : 1977

Maling HM, Saul W, Williams MA, Brown EAB, Gillette JR
On the mechanisms of the potentiation by beta adrenergic
agonists of paraquat toxicity in rats and mice
In: Biochemical Mechanisms of Paraquat Toxicity

(ed Autor AP) New York, Academic Press. 1977. 173-156.

Maling HM, Saul W, Williams MA, Brown EAB, Gillette JR
Reduced Body Clearance as the Major Mechanism of the
Potentiation by beta 2-Adrenergic Agonists of Paraquat
Lethality in Rats.

Toxic appl Pharmac 43 : 57-72 ; 1977

Mason RP, Peterson FJ, Callaghan JT, Holzman JL

Ascorbic Acid destruction of the O_2^- generated by nitrofurantoin and paraquat
free radicals

Pharmacologist 19 ; 192 : 1977

McGeown MG

Clinical Aspects of paraquat poisoning

In: Clinical Aspects of Paraquat Poisoning (ed K Fletcher)

London, ICI Ltd. 1977. 12-21.

Mirchev N

Acute Poisoning with Gramoxone (paraquat)

Vetr bol 16 ; 99-101 ; 1977

Montgomery MR

Paraquat toxicity and pulmonary superoxide dismutase: An
enzymic deficiency of lung microsomes.

Res Commun Chem Path Pharm 16 ; 155-8:1977

- 1977 (cont)

Montgomery MR & Mortenson GA
Inhibition of pulmonary mixed function oxidations
by paraquat and ozone
Toxic appl Pharmac 41; 183-4 : 1977

Natori H
Paraquat Lung
Respir Circ 25; 409-12 : 1977

Neoral L, Dusek J, Smysl B
A contribution to the pathogenesis of lethal paraquat poisoning
Z. Rechtsmed 80; 1-7 : 1977

Okahara T, Boye GL, Michelakis AM, Huang CT
Effect of paraquat on lung metabolism of PGE₂
Pharmacologist 19; 183 : 1977

Okonek S
Haemoperfusion with coated activated charcoal for treating acute intoxication
by drugs, plant protection agents
Med Klin 72; 862-6 : 1977

Okonek S & Hofmann A
Current Aspects of the therapy of paraquat and diquat poisoning:
Gut lavage, haemodialysis and haemoperfusion
In: Clinical Aspects of Paraquat Poisoning: (ed Fletcher K)
London, ICI Ltd. 1977. 55-68

O'Neil JJ Engelbrecht FM Wilson AGE
Paraquat uptake and distribution by rat lungs
Am Rev Resp Dis 115 (4); 234 : 1977

Park J, Proudfoot AT & Prescott LF
Paraquat Poisoning : A clinical review of 31 cases
In: Clinical Aspects of Paraquat Poisoning: (ed Fletcher K)
London, ICI Ltd. 1977. 46-54

Prochnicka B, Kwiecien-Glowacka E, Bialka J
A case of fatal poisoning with Gramoxone
Przegl Lekar 34; 511-2 : 1977 (Polish)

Reddy KA, Litov RE, Omaye ST
Effect of pretreatment with antiinflammatory agents on paraquat toxicity
in the rat
Res Commun Chem Path Pharm 17; 87-100 : 1977

Rhodes ML, Patterson CE
Effect of exogenous superoxide dismutase on paraquat toxicity
Clin Res 25; 592A : 1977

• 1977 (Cont)

Rose MS & Smith LL

The relevance of paraquat accumulation by tissues. In:
Biochemical Mechanisms of Paraquat Toxicity,
(ed Autor AP) New York, Academic Press. 1977. 71-91

Rose MS & Smith LL

Tissue uptake of paraquat and diquat
Gen Pharmacol 8; 173-6 : 1977

Seidenfeld J, Wycoff D, Zaval D, Richerson H
Paraquat lung injury in rabbits
Clin Res 25 (3); 423A : 1977

Smith LL & Rose MS

A comparison of the effects of paraquat and diquat on the
water content of rat lung and the incorporation of thymidine into
lung DNA

Toxicology 8; 223-230 : 1977

Smith LL, Rose MS

Biochemical changes in lungs exposed to paraquat: In:
Biochemical Mechanisms of Paraquat Toxicity,
(ed Autor AP) New York, Academic Press. 1977. 187-200

Smith LL, Rose MS & Wyatt I

The relevance of free radical formation in the rat
lung to the mechanism of paraquat toxicity
Proc Europ Soc Toxicol 18; 206-8 : 1977

Solfrank G, Mathes G, Clarmann M & Beyer KH

Haemoperfusion through activated charcoal in paraquat
intoxication

Acta Pharmac Tox 41 Supp 11; 91-101 : 1977

Sykes BI, Purchase IFW, Smith LL

Pulmonary ultrastructure after oral and intravenous dosage
of paraquat to rats.

J Path 121; 233-41 : 1977

Talcott RE, Shu H, Wei ET

Lipid peroxidation and paraquat toxicity

Fed Proc 36; 998 : 1977

Thomas PD, Thomas D, Chan Y-L, Clarkson AR

Paraquat poisoning is not necessarily fatal

Med J Aust 2; 564-5 : 1977

Vale JA & Goulding R

Paraquat poisoning : The unsuccessful vigorous treatment
of three patients

In: Clinical Aspects of Paraquat Poisoning (ed Fletcher K)
London, ICI Ltd. 1977. 22-33

• 1977 (Cont)

Vale JA, Crome P, Volans GN, Widdop B and Goulding R
 The treatment of paraquat poisoning using oral sorbents
 and charcoal haemoperfusion

Acta Pharmac Tox 41 Supp 11; 109-17: 1977

Widdop B, Medd RK, Braithwaite RA
 Charcoal haemoperfusion in the treatment of
 paraquat poisoning
Proc Europ Soc Toxicol 18; 156-9: 1977

Winchester JF, Maini R
 Paraquat removal by sorbents
 In: Clinical Aspects of Paraquat Poisoning (ed Fletcher K)
 London, ICI Ltd. 1977. 69-73

Witschi H, Kacew S, Hirai KI, Cote MG
 In vivo oxidation of reduced nicotinamide adenine
 dinucleotide phosphate by paraquat and diquat in rat lung
Chem Biol Interact 19; 143-160: 1977

Witschi H, Hirai KI, Cote MG
 Primary events in the lung following exposure to toxic chemicals
 In: Biochemical Mechanisms of paraquat toxicity
 (ed Autor AP) New York, Academic Press. 1977. 1-20.

• 1978

Ackrill P, Hasleton PS, Ralston AJ
 Oesophageal perforation due to paraquat
Br Med J 1; 1252-3: 1978

Adachi H, Yokata T, Fujihara S, Nakamura H, Uchino F.
 Two autopsy cases of paraquat poisoning
Tohoku J exp Med 125; 331-9: 1978 (Japanese)

Bassett DJP, Fisher AB
 Alterations of glucose metabolism during perfusion of rat lung with
 paraquat
Am J Physiol 234; E653-E659: 1978

Bier RK, Osborne IJT
 Pulmonary changes in paraquat poisoning
Radiology 127; 308: 1978

Bignami M et al
 In vitro mutagenicity studies of diquat and paraquat in salmonella,
 streptomyces and aspergillus.
Atti Assoc Genet Ital 23; 43-4; 1978 (Italian)

Block ER & Wasserman B
 Potentiation of acute paraquat toxicity by vitamin E deficiency.
Am Rev Resp Dis 117; 313: 1978

• 1978 (Cont)

Dearden LC Fairshter RD

Pulmonary ultrastructure of the late aspects of human paraquat poisoning
Am J Path 93; 667-680 : 1978

Dearnley DP Martin MFR

Plasmapheresis for paraquat poisoning
Lancet 1; 162 : 1978

Evers WD Hook JB & Bond JT

Increased sensitivity to paraquat in mice fed a purified diet versus a closed-formula diet.

Pharmacologist 20; 178 : 1978

Fairshter RD

Paraquat and Marihuana. Assessing the hazard
Chest 74; 357-8 : 1978

Fairshter RD

Paraquat Poisoning : An update
Western J Med 128; 56-58 : 1978

Firlik M

Changes in the respiratory system in paraquat poisoning
Medyayna Pracy 29; 325-8 : 1978

Fitzgerald GR

Paraquat Poisoning
J Irish Med Ass 71 326-7 1978

Fitzgerald GR Barniville G

Poisoning by granular paraquat
J Irish Phys Surg 7; 133-6 : 1978

Fitzgerald GR, Barniville G, Black J, Silke B

Paraquat poisoning in agricultural workers

J Irish Med Ass 71; 336-342 : 1978

Fitzgerald GR, Carmody M, Barniville G, O'Dwyer WF, Flanagan M, Silke B
The changing pattern of paraquat poisoning : An epidemiologic study

J Irish Med Ass 71; 103-8 : 1978

Ford JE

Paraquat toxicology and medical management
Vet & Human Toxicol 20; 465:

Gee BR, Farrow CS, White RJ, Orr J

Paraquat toxicity resulting in respiratory distress syndrome in a dog
J Am Anim Hosp Ass 14; 256-263 : 1978

George K, George M

Chromosome uncoiling effect of paraquat
Ind J exp Biol 16; 933-7 : 1978

• 1978 (cont)

Giri SN, Curry DL, Hollinger MA, Freywald & Scheidt M
 Effects of paraquat on plasma insulin & prostaglandin levels in rats
Pharmacologist 20; 156 : 1978

Giri SN, Krishna G
 The effects of paraquat on prostaglandin synthesis of guinea pig lungs
Toxicology 11; 345-351 : 1978

Greenberg DB, Lyons SA, Last JA
 Paraquat-induced changes in the rat of collagen biosynthesis by rat lung explants
J Lab Clin Med 92; 1033-1042 : 1978

Greenberg DB, Reiser KM, Last JA
 Correlation of biochemical and morphologic manifestations of acute pulmonary fibrosis in rats administered paraquat
Chest 74; 421-5 : 1978

Greenberg DB, Reiser KM, Lyons SA, Last JA
 Paraquat induced collagen biosynthesis by rat lung explants
Clin Res 26; A135 : 1978

Greig D, Streat SJ
 Intentional paraquat poisoning : Case report
NZ Med J 88; 12-13 : 1978

Hassan HM & Fridovich I
 Superoxide radical and the oxygen enhancement of the toxicity of paraquat in escherichia coli
J Biol Chem 253; 8143-8 : 1978

Hollinger MA, Giri SN
 Binding of radioactivity from (14) paraquat to rat lung protein in vitro
Res Commun Chem Path Pharm 19; 329-335 : 1978

Hollinger MA, Giri SN, Freywald M
 Effect of paraquat on zinc content of rat lung
Toxic appl Pharmac 43; 259 : 1978

Hollinger MA, Zuckermann JE, Giri SN
 Effect of acute and chronic paraquat on rat lung collagen content
Res Commun Chem Path Pharm 21; 295-305 : 1978

Howard JK
 Dermal exposure to paraquat
Lancet 1; 1100:1978

Howard JK
 Treatment of paraquat poisoning
Papua New Guinea Med J 21; 217-8:1978

- 1978 (cont)

Jaroš F
 Acute percutaneous paraquat poisoning
Lancet 1;275:1978

Jaros F, Zuffa L, Kratinova R & Skakala I
 Acute percutaneous intoxication by Gramoxone
Prac Lek 30 260-3 1978 (Czech)

Kelly DF, Morgan DG, Darke PGG, Gibbs C, Pearson H, Weaver MBQ
 Pathology of acute respiratory distress in the dog associated with
 paraquat poisoning
J Comp Path 88;275-294:1978

Kozler M
 Paraquat and living environment
Cesk Hyg 23 ;106-111: 1978 (Czech)

Kozler M
 Paraquat and diquat
Prac Lek 30 ;61-64 : 1978 (Czech)

Larsson B, Oskarsson A, Tjälve H
 On the binding of the bisquaternary ammonium compound paraquat to
 melanin and cartilage in vivo.
Biochem Pharmacol 27 ; 1721-4 : 1978

Last JA Reiser K Greenberg DB
 Correlation of biochemical and morphological manifestations of acute
 pulmonary fibrosis in rats administered paraquat
Clin Res 26 (3);A450: 1978

Lock EA, Ishmael J
 The effects of paraquat and diquat on rat kidney
Toxic appl Pharmac 45 abstr 21 p227 1978

Lunken C
 Repeated self-poisoning
Br Med J 2 ;1718 : 1978

Luty S, Cisak E, Latuszynska J & Przylepa E
 Investigations of the influence of paraquat on disturbances in
 embryonic & post-embryonic development of white rats.
Bromat Chem Toksykol 11 ; 159-165 : 1978 (Czech)

Luty S, Latuszynska J, Cisak E, Przylepa E
 The influence of paraquat on the internal organs of mice
Brom Chem Toks 11 ; 23-29 : 1978 (Czech)

Maling HM, Saul W, Williams MA, Brown EAD, Gillette JR
 Reduced body clearance as the major mechanism of the potentiation by B_2 -
 adrenergic agonists of paraquat lethality in rats
Toxic appl Pharmac 43 ; 57-72 : 1978

• 1978 (Cont)

Malmqvist E & Robertson B
 Biochemical changes in the surfactant system of the lung after
 paraquat poisoning.
Z Erkr Atmungsorgane 151;177-8:1978 (German)

Martens MA & Heyndrickx A
 Toxicology and treatment of paraquat intoxication.
Farm Tijdschr Belg 55;61-68:1978 (Flemish)

Matsuura N, Takinami M, Kurisaki E, Satoo H
 Distribution of paraquat dichloride and diquat dibromide in the living body
Fukushune Igakkai Zasshi 28 (3-4); 212:1978 (Japanese)
Pest. Abstr. 12 (6); 338-9:1979

McCormack K M, Gibson J E
 The renal handling on paraquat during development
 Proceedings of the First International Congress on Toxicology. Toxicology as a Predictive Science. (Ed GL Plaa WAM Duncan) N.Y. Acad Press. 1978. 442-443.

Meerbach VW, Grabner R
 Lung alterations after paraquat poisoning
Exp Path 16 ;168-179 : 1978

Miller J, Sanders E, Webb D
 Plasmapheresis for paraquat poisoning
Lancet 1 ;875-6 : 1978

Montgomery MR, Casey PJ, Niewoehner DE
 Acute effects of paraquat and ozone on cytochrome-dependant enzyme systems in the lung.
Toxic appl Pharmac 45 ;299:1978

Mukada T, Sasano N, Sato K
 Autopsy findings in a case of acute paraquat poisoning with extensive cerebral purpura
Tohoku J exp Med 125 ; 253-263 : 1978 (Japanese)

Netter KJ, Steffen CH
 Paraquat induced formation of hyperoxide in mouse liver microsomes
Br J Pharmacol 63 ; 351P-353P : 1978

Newhouse M, McEvoy D, Rosenthal D
 Percutaneous paraquat absorption : An association with cutaneous lesions and respiratory failure
Arch Dermatol. 114 ; 1516-9 : 1978

Ogata M & Hasegawa T
 The effect of paraquat on the mitochondrial energy transfer action.
Cell Struct Funct 3;325-330:1978

Omaye ST, Reddy KA, Cross CE
 Enhanced lung toxicity in selenium deficient rats
Toxic appl Pharmac 43 ; 237-247:1978

Pasi A
The toxicology of paraquat, diquat and morfamquat
 Zurich, Hans Huber 1978

• 1978 (Cont)

Popenoe D & Loosli CG

The morphological effects of a single exposure of paraquat on the mouse lung

Proc West Pharmacol Soc 21 ; 151-3 : 1978

Powell KE

A summary of pertinent medical information about paraquat in marihuana
J Tennessee Med 71 ; 681-2 ; 1978

Powell KE

The Big Furor : Paraquat on Marijuana

Vet Human Toxicol 20 ; 211-4 : 1978

Raffin TA, Robin ED, Pickersgill J, et al

Paraquat ingestion and pulmonary injury

West J Med 128 ; 26-34 : 1978

Raffin TA, Simon LH, Theodore J, Douglas W, Robin ED

Hypoxia protects type II pneumocytes (T-II-P) from paraquat toxicity

Clin Res 26;A453 : 1978

Rebello G, Mason JK

Pulmonary histological appearances in fatal paraquat poisoning

Histopathology 2 ; 53-66 : 1978

Rhodes ML, Patterson CE

Effect of exogenous superoxide dismutase on paraquat toxicity

Am Rev Resp Dis 117 ; 255:1978

Rossouw DJ & Engelbrecht FM

The influence of paraquat on the in vitro oxygen consumption of rabbit lung.

SA Med J 54;199-201:1978

Rossouw DJ & Engelbrecht FM

The effect of paraquat on the respiration of lung cell fractions.

SA med J 54;1101-4:1978

Schmitt SL & Autor AP

The accumulation of paraquat and diquat by isolated lung cells.

Pharmacol 20;Abstr 272:1978

Schmitt S L, Autor A P

Effect of paraquat on alveolar macrophages and type II pneumocytes isolated from rat lungs

Proceedings of the First International Congress on Toxicology.

Toxicology as a Predictive Science. (Ed. GL Plaa WAM Duncan)

New York, Academic Press. 1978. 595-596.

Seidenfeld JJ, Wycoff D, Zavala DC, Richerson HB

Paraquat lung injury in rabbits

Br J Ind Med 35 ; 245-257: 1978

- 1978 (cont)

Smith L L, Rose M S

The effect of low oxygen therapy on paraquat toxicity in rats
 Proceedings of the First International Congress on Toxicology.
 Toxicology as a Predictive Science. (Ed. GL Plaa WAM Duncan)
 New York, Academic Press, 1978. 443.

Spector D, Whorton D, Zachary J, Slavin R

Fatal paraquat poisoning : Tissue concentrations and implications for treatment

John Hopkins Med J 142 ; 110-3 : 1978

Steffen CH

Influence of paraquat in microsomal oxygen uptake
Naunyn-Schmiedberg Arch Pharmacol 302 (5) R20 1978

Takegawa K, Orita S, Kako K, Shiamura K, Matsumoto N & Miwa S
 A case of fatal paraquat poisoning.

Yamaguchi Igaku 27(4); 351:1978

Thompson WD, Patrick RS

Collagen prolyl hydroxylase levels in experimental paraquat poisoning
Br J exp Path 59 ; 288-291 : 1978

Verma SP & Bahga HS

Some Pharmacological Studies on Paraquat

Indian Vet J 55; 385-9:1978

Vucinovic B

Four Cases of Paraquat Poisoning treated in the Internal-Medicine Department of the General Hospital at Split.

Arh hig Rada 29; 261-5:1978 (Yugoslav)

Walters KA & Dugard PH

The Influence of Polyoxyethylene Ether Surfactants on Transport of Paraquat across isolated Gastric Mucosa.

J Pharm Pharmacol 30 (Suppl); 32P:1978

Warden JA, Rhodes ML, Patterson CE

Effect of expectorants on paraquat poisoning in rats

Am Rev Resp Dis 117 ; 264 : 1978

Warden JA, Rhodes ML

Failure of hypoxia to protect against paraquat toxicity in rats

Am Rev Resp Dis 117 ; 265 : 1978

Wasserman B, Block ER

Prevention of acute paraquat toxicity in rats by superoxide dismutase

Aviat Space Environ Med 49 ; 805-9 : 1978

Wright N, Yeoman WB, Hale KA

Assessment of seventy cases of paraquat poisoning

Br Med J 2; 396:1978

Zavala DC, Rhodes M L

An effect of paraquat on the lungs of rabbits : Its implications in smoking contaminated marijuana

Chest 74; 418-420:1978

• 1979

Anon

Treatment centres for paraquat poisoning
Lancet II;375-6:1979

Adamis Z

Effect of paraquat on macrophages in vitro and in vivo
Egeszsegstudomany 23;73-77:1979 (Hungarian)

Arany I

Effect of urethane, dimethylnitrosamine, paraquat and butylated hydroxy-toluene on aerobic lactic acid production of mouse lung and on the activity of the key enzymes of glycolysis

Egeszsegstudomany 23 (2); 142-6:1979 (Hungarian)

Barni Comaprini I

Application of an Electrochemical Method in the Diagnosis of Poisoning by Paraquat. Experimental Research and Toxicological Deductions.

Zacchia 15(2);173-184:1979 (Italian)

Bassett D J P, Fisher A B

Stimulation of the pentose cycle by paraquat in isolated perfused rat lungs
Physiologist 19;117:1979

Benigni R, Bignami M et al

Mutagenicity studies in salmonella, streptomyces, aspergillus and unscheduled DNA synthesis in EUE cells of paraquat and diquat
Mutat Res 64 (2);127-128:1979

Benigni R, Bignami M et al

Mutational studies with diquat and paraquat in vitro
Mutat Res 68 (3);183-193:1979

Bismuth C, Conso F, Wattel F, Gosselin B, Lambert H

Coated activated charcoal haemoperfusion: Experience of french anti-poison centres in 60 cases

Vet & Human Toxicol 21;81-83:1979

Block E R

Potentiation of acute paraquat toxicity by Vitamin E deficiency
Lung 156;195-203:1979

Block E R & Cannon J K

Paraquat-induced lipid peroxidation in isolated perfused rat lungs
Clin Res 27;A394:1979

Brigeluis R, Lengfeld E

Influence of cu-pencillamine on paraquat toxicity - investigation of lipid-metabolism in the isolated perfused rat-liver
Hoppe-Seyler's Z Physiol Chem 360 (9);1132:1979 (German)

• 1979 (Cont)

Burk RF, Lawrence RA, Lane JM & Hamm DP
 Lipid Peroxidation and Liver Necrosis in Selenium-deficient Rats given Diquat and Paraquat.
Gastroenterology 76;1109:1979

Castano P
 Acute Intoxication by Paraquat in Rats. Light and Electron Microscope Observations.
Med Lav 70(5); 375-387:1979

Conso F
 Paraquat poisoning - experience of poison control centres in France
Vet Hum Toxicol 21;(Suppl) 112:1979

Cravey R H
 Poisoning by paraquat
Clin Toxicol 14;195-8:1979

Dabir-Vaziri N, Ness R L, Fairshter R D, Smith W R, Rosen S M
 Nephrotoxicity of paraquat in man
Arch Int Med 139;172-4:1979

Davies D S & McManus M E
 The effect of paraquat on the covalent binding of radio-labelled DOPA to liver and lung microsomal protein
Br J Pharm 66;425P-426P:1979

De Lavaur E, Siou G, Grolleau G
 Comparative study of the action of diquat and paraquat on the digestive mucosa of mice, rats and rabbits
Ann Zool Ecol Anim 11 (2);159-169:1979 (French)

Diksmith T S S, Datta K K, Raizada R B, Kushwah H S
 Effect of paraquat dichloride in male rabbits
Ind J Exp Biol 17 (9);926-8:1979

Drew R & Gram T E
 Vehicle alteration of paraquat lethality in mice
Toxic appl Pharmac 48;479-487:1979

Drew R, Siddik Z H & Gram T E
 Uptake and efflux of ¹⁴C-paraquat by rat lung slices:
 The effect of Imipramine and other drugs
Toxic appl Pharmac 49;473-8:1979

Etherton J E, Gresham G A
 Early bronchiolar damage following paraquat poisoning in mice
J Path 128;21-27:1979

Fairshter R D, Dabir-Vaziri N, Smith W P, Glauser F L & Wilson A F
 Paraquat poisoning: an analytical toxicologic study of three cases
Toxicology 12;259-266:1979

Fischer H, Kahler J
 Lethal poisoning by paraquat - case report
Z fur Rechtsmedizin 84 (1);61:1979 (German)

• 1979 (Cont)

Fitzgerald G R, Barniville G, Dickstein K, Carmody M & O'Dwyer W F
Experience with Fuller's earth in paraquat poisoning
J Ir Med Ass 72;149-152:1979

Fitzgerald GR, Barniville G, Gibney RTN & Fitzgerald MX
Clinical, Radiological and Pulmonary Function Assessment in 13
Long-term Survivors of Paraquat Poisoning
Thorax 34;414-429:1979

Fridovich I & Hassan HM
Paraquat and the Exacerbation of Oxygen Toxicity
Trends in Biochem Sci 4;113-5:1979

Giri S N, Curry D L, Hollinger M A, Freywald M
Effect of paraquat on plasma enzymes, insulin, glucose
and liver glycogen in the rat
Environ Res 20 (2);300-308:1979

Giri S N, Hollinger M A
Inhibitory effect of paraquat on histamine and isoproterenol
induced changes of cyclic-nucleotides in rat lung slices
Experientia 35 (9);1219:1979

Giri S N, Hollinger M A, Schiedt M J
The failure of superoxide dismutase to modify paraquat-induced
increased pulmonary vascular permeability and edema in mice
Am. rev Resp. Dis. Suppl. 119;217:1979

Goldstein B D, Rozen M G, Quintava J C, Amoruso M A
Decrease in mouse lung and liver glutathione peroxide acitivity
and potentiation of the lethal effects of ozone and paraquat by
the superoxide dismutase inhibitor diethyldithiocarbamate
Biochem Pharmacol 28;27-30:1979

Griffin M, Smith L L, Wynne J
Changes in transglutaminase activity in an experimental model of pulmonary
fibrosis induced by paraquat
Br J Exp Path 60;653-661:1979

Haley T J
Review of the toxicology of paraquat (1,1'dimethyl-4,4'-bipyridinium
chloride)
Clin Toxicol 14 1-46 1979

Higenbottom T, Crome P, Parkinson C & Nunn J
Further clinical observations on the pulmonary effects of paraquat
ingestion
Thorax 34;161-5:1979

• 1979 (Cont)

Hollinger M A, Raabe O G, Giri S N, Freywald M & Teague S V
Effect of the inhalation of zinc and dietary zinc on paraquat toxicity
in the rat
Toxic appl pharmac 49;53-61:1979

Howard J K
Recent experience with paraquat poisoning in Great Britain
- a review of 68 cases
Vet Hum Tox 21;213-216 Supplement:1979

Howard J K
A clinical survey of paraquat formulation workers
Br J Ind Med 36;220-3:1979

Hudson R H, Haegle M A & Tucker R K
Acute oral and percutaneous toxicity of pesticides to mallards:
Correlations with mammalian toxicity data
Toxic appl Pharmac 47;451-460:1979

Hussain M Z, Bhatnagar R S
Involvement of superoxide in the paraquat-induced enhancement
of lung collagen synthesis in organ culture
Biochem Biophys Res Commun 89;71-76:1979

Isoda N
A fatal case of intoxication due to paraquat dichloride
Nippon Noson Igaku Zasshi 28 (1);85-6:1979 (Japanese)

Iwinsky H, Winsel K
Veränderungen biochemischer prozesse der lunge unter der
Einwirkung von Schadstoffen
Z Erkr Atmungsorg 153 (1);142-9:1979 (German)

Johansson A & Cramner P
Alveolar macrophages from paraquat exposed rabbits. A study by
x-ray. Microanalysis after oxygen plasma microincineration
J Ultrastruct Res 66;85-86:1979

Kawai M
Experimental Studies on the Treatments of Acute Intoxication due to
Paraquat.
Nippon Noson Igakkai Zasshi 28(3);476-477:1979 (Japanese)

Kawatomi M, Koga H, Yokoyama K, Fujimatsu S et al
A Case of Autopsy of a Person who died of Paraquat Intoxication.
Nippon Naika Gakkai Zasshi 68(10);1332-3:1979 (Japanese)

- 1979 (Cont)

Kehrer JP, Haschek W & Witschi H
 The Influence of Hyperoxia on the Acute Toxicity of Paraquat
 and Diquat.
Drug Chem Tox 2(4);397-408:1979

Kozler M
 Dermal intoxication with paraquat and intoxication after inhalation
 of diquat aerosol
Prakt Lek 59 (8);312-3:1979 (Czech)

Kunc L, Kuncova M, Soldan F, Holusa R, Ahtaliko L
 Interaction of paraquat with lung surfactant
Bull Eur Physiopath Respir 15 (6);71:1979

Kuncova M, Kunc L, Soldan F, Holusa R
 Lung surface tension and morphology in rats after paraquat poisoning
Prac Lek 31 (4);126-131:1979 (Czech)

Kurisaki E, Sato H, Nagamori H
 The effect of paraquat on cultured human embryonic cells
J Toxicol Sci 4 (2);99-104:1979

Kurisaki E, Sato H
 Tissue distribution of paraquat and diquat after oral administration
 in rats
Forensic Sci Int 14 (3);165:1979

Kuttan R, Langranconi M, Sipes IG, Meezan E & Brendel K
 Effect of Paraquat Treatment on Prolyl Hydroxylase Activity and
 Collagen Synthesis of Rat Lung and Kidney.
Res Commun Chem Path Pharm 25;257-268:1979

Kuttan R, Spall R, Sipes IG, Meezan E & Brendel K
 Effect of Paraquat Treatment on Rat-kidney Basement-membranes
Toxic appl Pharmac 48 A177 1979

Lam HF, Takezawa J & Van Stee EW
 The effects of paraquat and diquat on lung function measurements
 in rats
Am Rev Resp Dis Suppl 119;327:1979

Levin PJ, Klaff LJ, Rose AG & Ferguson AD
 Pulmonary Effects of Contact Exposure to Paraquat: A Clinical
 and Experimental Study.
Thorax 34;150-160:1979

Lock EA
 The Effect of Paraquat and Diquat on Renal Function in the Rat.
Toxic appl Pharmac 48;327-336:1979

- 1979 (Cont)

Lock EA & Ishmael J

The Acute Effects of Paraquat and Diquat on the Rat Kidney.
Toxic appl Pharmac 50;67-76:1979

Manzo L, Gregotti C, DiNucci A & Richelmi P

Toxicology of Paraquat and Related Bipyridyls: Biochemical, Clinical and Therapeutic Aspects

Vet Human Toxicol 21;404-410:1979

Mastrangelo F, Lopez T, Rizzelli S, Maniso G, Corliano C, Alfonso L
 Hemodialysis and Hemoperfusion in the Treatment of Paraquat and Diquat Poisoning

Kidney Int 16(5);652:1979

Mastrangelo F, Rizzelli S, Maniso G et al

Nephropathy in paraquat and diquat acute poisoning

Minerva Nefrol 26 (2);135-8:1979 (Italian)

Matsuoka Y, Nakayama T et al

A Treated Case of Acute Paraquat Dichloride Intoxication

Nippon Noson Igaku Zasshi 28(1);58:1979 (Japanese)

Mayama S, Haneda T, Shimazu W, Kumakura M & Kohata T

A Case of Acute Poisoning by Gramoxone (herbicide)

Nippon Naika Gakkai Zasshi 68(5);559-560:1979 (Japanese)

Miura O, Sasaki S, Kagaya S, Watabe K & Sugaya H

Residue of Paraquat in Organs of Three Patients Intoxicated by Paraquat in 1978.

Akita Noson Igakkai Zasshi 26(1);86-7:1979 (Japanese)

Montgomery MR, Casey PJ, Valls AA, Cosio MG & Niewoehn DE

Biochemical and Morphological Correlation of Oxidant-induced

Pulmonary Injury - Low-dose Exposure to Paraquat, Oxygen and Ozone.

Arch Environ Hlth 34(6);396-401: 1979

Nagase H, Kimura K, Yajima M, Sato S & Aihara K

Experimental Studies on the Fibrotic Inflammation of Alveolar Wall due to Inhalation of Paraquat Dichloride. First Report

Nippon Kaimeni Gakkai Zasshi 10(1);90-3:1979 (Japanese)

Pest Abstr 13(4); 80-1136:1980

Nagase H, Kimura K, Yajima M, Sato S & Aihara K

Experimental Studies on the Fibrotic Inflammation of Alveolar Wall due to Inhalation of Paraquat Dichloride. Second Report

Nippon Kaimeni Gakkai Zasshi 10(2);149-151:1979 (Japanese)

Pest Abstr 13(4); 80-1137:1980

Nishimura H, Nishimura N & Oshima H

Experimental Studies of the Toxicity of Herbicide Pg II

Aichi Ika Daigaku Igakkai Zasshi 7(3); 197-202:1979 (Japanese)

Okonek S, Tonnis HJ, Baldamus CA, Hofmann A

Hemoperfusion versus Hemodialysis in the Management of Patients

severely poisoned by Organophosphorus Insecticides and Bipyridyl Herbicides.

Artific Organs 3(4);341:1979

• 1979 (Cont)

Okonek S, Baldamus CA, Hofmann A, Schuster CJ, Bechstein PB & Zoller B
Two Survivors of Severe Paraquat Intoxication by "Continuous
Haemoperfusion"
Klin Wschr 57;957-9:1979 (German)

Patterson CE & Rhodes ML
Continuous Intravenous Superoxide Dismutase Infusion in Paraquat
Toxicity.
Am rev Resp Dis(Suppl) 119;346:1979

Popenoe D
Effects of Paraquat Aerosol on Mouse Lung
Arch Path Lab med 103;331-4:1979

Popovic M & Leskovac V
Influence of Paraquat on Porcine Erythrocytes
Acta Pharm Jugoslav 29;19-22:1979 (Jugoslav)

Pratt IS, Keeling PL & Smith LL
Effect of High-concentrations of Oxygen on the Toxicity of
Paraquat & Diquat in Rats
Toxic appl Pharmac 48;A59:1979

Proudfoot AT, Stewart MS, Levitt T & Widdop B
Paraquat poisoning: significance of Plasma-Paraquat Concentrations
Lancet II;330-2:1979

Purser DA & Rose MS
The Toxicity and Renal Handling of Paraquat in Cynomologus Monkeys
Toxicology 15(1);31-41:1979

Ross JH, Kreiger RI
Structure Activity Correlations of Paraquat Homologs in the
Inhibition of Aldrin Epoxidation by Rat-liver Microsomes.
Toxic appl Pharmac 48;A80:1979

Ross WE, Block ER & Chang RY
Paraquat-induced DNA Damage in Mammalian-Cells
Biochem Biophys Res Commun 91 (4);1302-1308:1979

Roth RA, Wallace KB, Alper RH & Bailie MD
Effect of Paraquat Treatment of Rats on Disposition of 5-Hydroxy-
tryptamine and Angiotensin I by Perfused Lung
Biochem Pharmacol 28;2349-55:1979

Roussouw DJ & Engelbrecht FM
The Effect of Paraquat on the Aerobic Metabolism of Rabbit Alveolar
Macrophages and Lung Fibroblasts
S Afr Med J 55;20-3:1979

Roussouw DJ & Engelbrecht FM
Effect of Oxygen and Paraquat on the ¹⁴C-glucose Oxidation of
Rabbit Alveolar Macrophages and Lung Slices
S Afr med J 55;558-60:1979

• 1979 (Cont)

Shu H, Talcott RE, Rice SA & Wei ET
Lipid Peroxidation and Paraquat Toxicity
Biochem Pharmac 28;327-331:1979

Siddik Z H, Drew R & Gram T E
The effect of chlorpromazine on the uptake and efflux of paraquat
in rat lung slices
Toxic appl Pharmac 50;443-450:1979

Smith L L, Rose M S, Wyatt J
The pathology and biochemistry of paraquat
Ciba Foundation Series 65;321-341:1979

Steffen C, Netter K J
Mechanism of paraquat action on microsomal oxygen reduction and its relation
to lipid peroxidation
Toxic appl Pharmac 47;593-602:1979

Steffen C, Konder H
Absorption of paraquat by rat gut in vitro. Regional Differences
Arch Tox 43;99-103:1979

Ueda T, Fuzikawa H, Nohara T & Takamata H
Electron Cytochemical Study on the Damage of the Rat-Liver
by Paraquat
Acta Histochem Cytochem 12(6);612:1979

Van den Heede M, Heyndrickx A & Timperman J
Fatal Intoxication due to Paraquat taken without any Specific
Treatment
J Pharm Belg 34(2);69:1979 (French)

Vaziri ND, Ness RL, Fairshter RD, Smith WR & Rosen SM
Nephrotoxicity of Paraquat in Man
Arch Intern Med 139 ; 172-4:1979

Vesely DL, Watson B & Levey GS
Activation of Liver Guanylate Cyclase by Paraquat: Possible
Role of Superoxide Anion
J Pharm exp Ther 209;162-4:1979

Waight JJ & Wheater RH
Fatal percutaneous paraquat poisoning.
J Am med Ass 242(5); 472:1979

Wanatabe T, Sakai Y, Sotoyama Z, Veno M & Wanatabe M
Eye Damage due to the Herbicide Gramoxone (Paraquat)
Ganka Rinsho Iho 73(6);660:1979 (Japanese)

- 1979 (Cont)

Watanabe I, Sakai K, Toyama K, Ueno M, Watanabe M
 On Three Cases of Ocular Disturbance due to Gramoxon, A Herbicide containing 24% Paraquat Dichloride.
Ganka Rinsho Iho 73(10); 1244-1246:1979.(Japanese)

Withers EH, Madden JJ & Lynch JP
 Paraquat Burn of the Scrotum and Perineum
J Tenn Med Ass 72;109:1979

- 1980

Adam R J
 Non-fatal Disease due to Inhalation of Nebulised Paraquat
Brit med J 280(6222);1120-1121:1980

Asano Y, Yoshida K
 Effectiveness and limitations of haemoperfusion in patients intoxicated by paraquat dichloride
Nippon Noson Igakkai Zasshi 29(3);544-5:1980] (Japanese)
Pest Abstr 14(1);146:1981

Baudot P
 Comparative Toxicology of Bipyridylum-derived Herbicides:
 Paraquat and Diquat. Part 1.
Lyon Pharm 31(1);7-17:1980 (French)

Block ER & Cannon JK
 Paraquat induced Lipid Peroxidation in Isolated Perfused Rat Lungs.
Am Rev Resp Dis Suppl 121(4);314:1980

Brigelius R & Hashem A
 Inhibition of Paraquat-induced Lipid Peroxidation by the Superoxide-Dismutase Active Copper Complex CuTyr Z in the Isolated Perfused Rat Liver
Hoppe-Seyler's Z Physiol Chem 361(3);225:1980 (German)

Brown EAB & Maling HM
 Effects of Paraquat and Related Herbicides on the Acetylcholinesterase of Rat Lung.
Biochem Pharmacol 29(3);465-6:1980

Burk RF, Lawrence RA & Lane JM
 Liver Necrosis and Lipid Peroxidation in the Rat as the Result of Paraquat and Diquat Administration - Effect of Selenium Deficiency.
J Clin Invest 65(5);1024:1980

Calabrese EJ, Moore GS & Ho S
 Low Glucose-6-phosphate dehydrogenase activity and increased sensitivity to paraquat toxicity.
Bull Environ Contam Tox 24(3);369-373:1980

• 1980 (Cont)

Dasta JF

Management of paraquat poisonings

Clinical Toxicology Consultant 2(1);11-20:1980

Deveckova D, Mydlik M

Gramoxone ocular burns

Cesk Oftalmol 36(1);7-10:1980 (Czech)

Forman HJ, Nelson J, Fisher AB

Rat alveolar macrophages require NADPH for superoxide production in the respiratory burst. Effect of NADPH depletion by paraquat

J Biol Chem 255(20);9879-83:1980

Garnier R, Conso F, Efthymiou ML, Fournier E

Toxicity of paraquat by inhalation

Arch Mal Prof 41(1);21-22:1980 (French)

Garnier R, Conso F & Efthymio ML

Paraquat Toxicity in Occupational Setting.

Med Leg Toxicol 23(3);131:1980 (French)

George M & Hedworth-Whitty RB

Non-fatal Lung Disease due to Inhalation of Nebulised

Paraquat

Brit med J 280(6218);902:1980

Giri SN & Krishna GA

The Effect of Paraquat on Guanylate-cyclase Activity in Relation to Morphological-changes of Guinea Pig Lung

Lung 157(3);127:1980

Giri SN, Hollinger MA

Effects of lung toxins on PGF₂ and PGE₂ levels in plasma and combined pleural effusion and lung lavage of rats

Adv Prostaglandin Thromboxane Res 7;953-6:1980

Grant HC, Lantos PL & Parkinson C

Cerebral Damage in Paraquat Poisoning

Histopathology 4(2);185-195:1980

Hart B

Non-fatal Lung Disease due to Inhalation of Nebulised Paraquat

Brit med J 281(6232);63-4:1980

Harvey J, Palmer D

Pulmonary complications of ingestion of the herbicide paraquat: a case report

Respir Care 25(5);573-575:1980

Hayashi S, Arai Y, Kondo T et al

Two Cases of Intoxication due to Paraquat Dichloride

Nippon Naika Gakkai Zasshi 69(11);1486-7:1980 (Japanese)

- 1980 (Cont)

Hirai K, Ogawa K

Pulmonary type-II cell injuries and inhibition of cytochrome-oxidase activity by diquat and paraquat
J Electron Microsc 29(3);339:1980

Hollinger MA, Patwell SW, Zuckerman JE, Gorin AB, Parsons G & Giri SN
Effect of Paraquat on Serum Angiotensin converting Enzyme
Am Rev Resp Dis 121(5); 795-8:1980

Howard JK

Paraquat: a review of worker exposure in normal usage
J Soc Occup Med 30(1);6-11:1980

Howard J K

Paraquat poisoning: UK experience and its therapeutic implications

In: Proceedings of First Paraquat Poisoning Study Meeting
Tokyo, ICI Ltd, 1980. 37-42

Howard J K

Sabapathy NN, Whitehead PA

Effects of long term exposure to paraquat

Toxicol letters Suppl 1; 49 : 1980

Howard J K

Sabapathy NN, Whitehead PA

An evaluation of the long term affects of paraquat spraying.

In: Proc Eighth Internat Confon Occup Hlth in Chem Indust

Ed. N Takamura, Y Yamamura. Tokyo Aikawa Publ Co, 1980. 307 - 311

Kim SJ & Roberts JF

Angiotensin converting Enzyme Activity in Paraquat-treated Mice Lungs.

Am Rev Resp Dis Suppl 121(4);242:1980

Kornbrust DJ & Mavis RD

The Effect of Paraquat on Microsomal Lipid Peroxidation in vitro and in vivo.

Tox Appl Pharmac 53(2); 323-332:1980

Kovanen H, Haltia M & Cantell K

Non-fatal Lung Disease due to Inhalation of Nebulised Paraquat.

Brit med J 280 (6218); 902:1980

Lam H F, Takezawa J, Gupta B N, Van Stee E W

A comparison of the effects of paraquat and diquat on lung compliance, lung volumes and single breath diffusing capacity in the rat

Toxicology 18(2);111-123:1980

Malmqvist E

The Influence of Paraquat on the in vitro Incorporation of Lecithin Precursors in Lung Tissue and Alveolar Leithin

Scand J Clin Lab Invest 40(3); 233-239:1980

- 1980 (Cont)

Matkovics B, Szabo L Varga SzI, Novak R, Barabas K & Berensa Gr
In vivo Effects of Paraquat on some Oxidative Enzymes of Mice.
Gen Pharmacol 11(3);267-270:1980

Matkovics B, Barabas K, Szabo L, Berencsi G
In vivo study of the mechanism of protective effects of ascorbic acid and reduced glutathione in paraquat poisoning
Gen Pharmacol 11(5);455-462:1980

Matsumoto T, Matsumori H, Kuwakara N, Fukuda Y, Ariwa R
A histopathological study of the liver in paraquat poisoning - an analysis of fourteen autopsy cases with emphasis on bile duct injury
Acta Pathol Japonica 30(6);859-870:1980

McManus ME, Davies DS
Paraquat-stimulated binding of dopa to liver and lung microsomal protein
Xenobiotica 10(10);745-752;1980

Montgomery MR, Wyatt I, Smith LL
Oxygen effects on metabolism and paraquat uptake in rat lung slices
Exp Lung Res 1(3); 239-250:1980

Mullick FG, Ishak KG, Mahabur R & Stromeye FW
Hepatic-injury associated with Paraquat Toxicity in Humans.
Lab Invest 42(1);138 : 1980

Muramatsu H, Shiga T et al
Effect of a herbicide paraquat or diquat on cultured human fetal cells
Fukushima Igaku Zasshi 30(1-2) 173 1980
Pestic Abstr 14 (4) 1106 1980

Okahata S
Mechanism of methyl viologen induced hemolysis
Hiroshima J Med Sci 29(2);49-54:1980 (Japanese)

Okawada N, Yagasaki K & Kondo T
Ocular impairments due to an agricultural pesticide.
Nippon Noson Igakkai Zasshi 29(3);550-1:1980 (Japanese)

Okonek S, Baldamus CA, Hofmann A
Survival despite potentially fatal plasma paraquat concentrations
The Lancet II (8194);589:1980

Omaye ST, Reddy AK
Early and delayed biochemical effects of paraquat toxicity on rat lung
Exp Molec Path 33(1);65-73:1980

Parkinson C
The Changing Pattern of Paraquat Poisoning in Man
Histopathology 4(2);171-183:1980

• 1980 (Cont)

Raffin TA, Robin ED, Simon LM, Douglas WHJ, Theodore J
 The Effects of Variable Oxygen Tension and of Exogenous Superoxide
 Dismutase on Type II Pneumocytes exposed to Paraquat.
Lab Invest 42(2);205-8:1980

Saunier C, Horsky P et al
 Pentose pathway in pulmonary fibrosis due to chronic paraquat poisoning
Respiration 40(2);69:1980

Selypes A, Nagymajtenyi, Berencsi G
 Mutagenic and embryotoxic effects of paraquat and diquat
Bull Environ Contam Tox 25;513-517:1980

Smith L L
 The pathology and biochemistry of paraquat in the lung
 In: Proceedings of First Paraquat Poisoning Study Meeting.
 ICI Ltd, 1980. 43-54

Steffen C, Muliawan H & Kappus H
 Lack of in vivo Lipid Peroxidation in Experimental Paraquat
 Poisoning
Arch Pharmacol 310(3);241-3:1980

Stokke T, Burchard H, Kemper N, Rahlf G, Rohrborn W & Atthai D
 Case of 30 Days Survival after ingesting 30g Paraquat -
 Treatment of Serial Studies of Lung-function
Intensive Care Med 6(1);26:1980 (German)

Sugaya H, Ohe T, Ueno T et al
 Clinical discussion on six cases of paraquat dichloride intoxication
Nippon Naika Gakkai Zasshi 69(7);876:1980 (Japanese)
Pest Abstr 13(11);3219:1980

Tsuzuki K, Tanabe Y, Sato C et al
 Charcoal Hemoperfusion of an Infantile Case of Accidental Paraquat
 Dichloride Intoxication
Shonika 21(13); 1591-1594:1980 (Japanese)

Waddell WJ, Marlowe C
 Tissue and cellular disposition of paraquat in mice
Tox Appl Pharmacol 56(1);127-140:1980

Webb DB
 The Autoradiographic Localization of Paraquat in the Lung.
Brit J Exp Path 61(2);217-221:1980

• 1981

Beretta C, Fadini L, Montesis C et al
 Membrane lipid composition of subcellular fractions from lungs of
 rats treated with paraquat.
Pharmacol Res Commun 13(5);433-442:1981

- 1981 (Cont)

Brigelius R & Anwer MS
 Increased biliary GSSG secretion and loss of hepatic glutathione in isolated perfused rat liver after paraquat treatment.
Res Comm Chem Pathol Pharmacol 31(3);493-502:1981

Brigelius R, Hashem A & Lengfelder E
 Paraquat induced alterations of phospholipids and GSSG-release in the isolated perfused rat liver, and the effects of SOD-active copper complexes.
Biochem Pharmacol 30(4); 349-354:1981

Carmines EL, Carchman RA & Borzelleca JF
 Investigations into the mechanism of paraquat toxicity utilising a cell culture system.
Toxicol Appl Pharmacol 58(3);353-362:1981

Engelbrecht FM, Rossouw DJ & Nienaber MW
 The effect of paraquat on the incorporation of ¹⁴C-leucine and ¹⁴C-palmitate into lung proteins and lung lipids of rats and rabbits.
South African Med J 59(26);953-961:1981

Howard JK, Sabapathy NN & Whitehead PA
 A study of the health of Malaysian plantation workers with particular reference to paraquat spraymen.
Br J Ind Med 38(2);110-116:1981

Haworth GM, Bennett PN & Davies DS
 Kinetics of paraquat elimination in the dog.
Tox Appl Pharmacol 57(2);139-145:1981

Longstaff JS, Humphreys DJ, Hayward AHS & Stodulski JBJ
 Paraquat poisoning in dogs and cats - differences between accidental and malicious poisoning.
J Sm Anim Pract 22(3);153:1981

Mastrangelo F, Rizzelli S, Manisco G et al
 Nephropathy in paraquat and diquat acute poisoning.
Minerva Nefrol 26(2);135-8:1979 (Italian)

Nagase H
 An experimental study of the fibrosing alveolitis induced by paraquat administration.
Nippon Kaimen Igakkai Zasshi 10(2);112-136:1979 (Japanese)

Ross JH & Krieger RI
 Structure activity correlations of amines inhibiting active uptake of paraquat (Methyl Viologen) into rat lung slices.
Toxicol Appl Pharmacol 59;238-249:1981

Smith LL & Wyatt I
 The accumulation of putrescine into slices of rat lung and brain and its relationship to the accumulation of paraquat.
Biochem Pharmacol 30(10); 1053-1058:1981

• 1981 (Cont)

Smith LL, Wyatt MS & Rose MS
Factors affecting the efflux of paraquat from rat lung slices.
Toxicology 19(3);197-207:1981

Walters KA, Dugard PH & Florence AT
Non-ionic surfactants and gastric mucosal transport of paraquat
J Pharm Pharmacol 33(4);207-213:1981

Webb DB & Davies CG
Paraquat poisoning and kidney function tests.
The Lancet I (8235); 1424:1981

Wyatt I, Doss AW, Zavala DC & Smith LL
Intrabronchial instillation of paraquat in rats: lung morphology
and retention study
Br J Ind Med 38(1);42-8:1981
